

High-Level Meeting Summary

The Leadership Team overseeing the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership convened to review progress made since its previous meeting on June 3, 2020. Drs. Francis Collins and Paul Stoffels, Co-Chairs of the Leadership Team, opened the meeting by highlighting the renewed urgency of ACTIV's work given the recent rise in cases, particularly in the United States. The Leadership Team reviewed progress on action items from previous meetings; discussed a new data sharing initiative led by the COVID-19 R&D Consortium; and heard updates from Co-Chairs of all four ACTIV Working Groups (WGs), which cover the following focus areas: (1) Preclinical; (2) Therapeutics Clinical (TX-Clinical); (3) Clinical Trial Capacity (CTC); and (4) Vaccines. The Leadership Team discussed progress made by each WG and reviewed ACTIV's planned activities for July.

New Action Items

Action	Owner
1. ACTIV Leadership Team private sector members are asked to recommend resources to support outreach to underserved communities for COVID-19 clinical trials and send to Michael Santos (b) (6)	ACTIV Leadership Team Members
2. Evaluate potential for natural history studies and connect Gary Gibbons with the appropriate COVID-19 Evidence Accelerator contact	Andy Plump

Progress on Action Items from Previous Meetings

David Wholley, MPhil, Senior VP of Research Partnerships, FNIH

The Leadership Team reviewed ongoing and completed action items from previous meetings, which are summarized by the tables below. Participant comments on specific action items are summarized beneath the tables where relevant.

Ongoing Action Item Review

	Action	Owner	Date Initiated	Progress Notes
1	Help coordinate efforts to reach out to populations for participation in vaccine and outpatient therapeutic trials	Francis Collins, NIH	6/17 Executive Committee Meeting	In Process – update today
2	Develop a viral strain that can be used for Preclinical testing and follow-up with (b) (4)	ACTIV Preclinical Working Group	6/17 Executive Committee Meeting	In Process – update today
3	Consider further the request to establish a potential additional ACTIV workstream to create a centralized data warehouse/cloud infrastructure for sharing clinical trials and real-world evidence data on COVID; or whether simply to partner with other initiatives in this area	Francis Collins, NIH; Michelle Culp; COVID-19 R&D Consortium	6/17 Executive Committee Meeting	In Process – update today
4	Set metrics related to cycle times and benchmarks for improvement in order to accelerate the preclinical space	Preclinical Working Group	6/3 Leadership Team Meeting	Metrics were added to the Preclinical WG manuscript currently in preparation, with planned submission week of July 6
5	Contact the (b) (4) to encourage the (b) (4) results to allow inclusion in the NCATS Open Science Data portal and analysis of screening results from previous screening campaigns	Francis Collins, ACTIV Executive Committee	5/20 Executive Committee Meeting	Previous arrangements make this not possible
6	Consider whether prize competitions using the data in the NCATS Portal are possible to entice others not involved in drug discovery	John Young, Preclinical Working Group	5/20 Executive Committee Meeting	Prize competitions are being considered as part of the WG's data infrastructure and sharing strategy

Regarding action item 5, Dr. Collins noted that the (b) (4) results database cannot be shared with ACTIV via the NCATS OpenData Portal because of contractual restrictions that predate the pandemic. The below sections of this document contain updates on action items 1, 2, and 3 from the Vaccines WG, the Preclinical WG, and Dr. Andrew Plump, respectively.

Completed Action Item Review

	Action	Owner	Date Initiated	Progress Notes
1	Share manuscript on SARS-CoV-2 controlled human infection model issues with EC	David Wholley, FNIH	6/17 Executive Committee Meeting	Complete – manuscript now accepted for publication
2	Determine expectations for longer-term sustainability of the inventories (e.g., both sites and innovations) to share with the Clinical Trial Capacity Working Group	Francis Collins, NIH; ACTIV Executive Committee	6/17 Executive Committee Meeting	Complete – NCATS will support data CTC WG dashboard and associated data
3	Share the Preclinical and Therapeutics Clinical survey link with HEVER and the R&D Consortium to broaden the reach of respondents	Preclinical and Therapeutics Clinical Working Groups	6/3 Leadership Team Meeting	Complete
4	Establish benchmark of preclinical assessment (including assays, graduating criteria, etc.) for mAb combinations and cocktails and if possible, receive input by the June 9 Summit	Preclinical and Therapeutics Clinical Working Groups	6/3 Leadership Team Meeting	Complete
5	Send the SARS-CoV-2 controlled human infection model draft manuscript to Tony Fauci for his feedback	Doug Lowy, Vaccines Working Group	5/20 Executive Committee Meeting	Complete
6	Draft a document formally replying to the Therapeutics Clinical Working Group on the issues raised in their May 4 letter to the Executive Committee, for Executive Committee review	David Wholley, FNIH Team	5/20 Executive Committee Meeting	Complete – verbal updates have been given instead
7	Consider developing criteria and a recommended workflow for the preclinical testing required to determine if a molecule is ready to bring into the clinic (both rapid/meets minimum criteria in the short term and especially the more robust processes required for the longer term)	Preclinical Working Group	5/20 Executive Committee Meeting	Complete – pandemic mode development testing is incorporated into a journal article being submitted to provide guidance to the field

The *New England Journal of Medicine* will publish the Vaccines WG's article on SARS-CoV-2 controlled human infection models (CHIMs) on July 1. The publication concludes that CHIMs will not accelerate vaccine development but may become useful later for further studying the virus.

Update on Data Sharing Initiative

Francis Collins, PhD, MD, Director, NIH; Andrew Plump, MD, PhD, President, Research and Development, Takeda

Representatives of the COVID-19 R&D Consortium, the Gates Foundation, (b) (4) and ClinicalTrials.gov are discussing ways to leverage existing data sharing platforms to facilitate exchange and analysis of COVID-19 clinical trial data (i.e., trial metadata, summary-level statistics, and anonymized patient-level data). (b) (4)

(b) (4)

(although Dr. Plump noted that no data have yet been added). Dr. Collins noted that, (b) (4), further efforts aim to streamline the process of depositing such data at ClinicalTrials.gov, and to create a path through which these data can be accessed (b) (4)

The COVID-19 R&D Consortium has also identified (b) (4) as the preferred platform for sharing patient-level data from both investigational and control arms of COVID-19 clinical trials. (b) (4) for data sharing among COVID-19 R&D companies (for both summary-level and patient-level data), and R&D Consortium members are developing metadata elements for COVID-19 trials and aligning on summary-level reporting protocols.

ACTIV representatives are involved in these discussions, and NIH officials viewed a demonstration (b) (4) on June 26 and will view a demonstration of the (b) (4) on July 7. NIH will request to review the (b) (4) to ensure that they include appropriate data sharing and privacy standards that would allow NIH personnel and extramural investigators conducting COVID-19 trials to access data through these platforms.

Discussion

Dr. (b) (6) highlighted the need to monitor post-recovery patients (b) (5) and asked whether (b) (5) to aid those efforts. Dr. Plump (b) (5) connect Dr. (b) (6) with individuals at the (b) (4) who may know more. Dr. (b) (6) stressed that longitudinal patient follow-up would also be crucial in the context of vaccine trials.

Preclinical WG

Christine Colvis, PhD, National Center for Advancing Translational Sciences (NCATS); John Young, PhD, Roche

Since the last Leadership Team meeting, the Preclinical WG has completed first drafts of both its Pandemic Response Drug Development SOP and its Animal Model manuscripts (both of which will be submitted to *Cell Host & Microbe*); created a site management structure for a virtual preclinical in vitro and in vivo testing network for therapeutic sponsors to access limited BSL 3/4 facilities (sites have been asked to confirm willingness to participate by July 15); received approximately 40 Preclinical/Clinical Data Survey responses supplying agents for consideration during ongoing Wave 2 Agent Prioritization of antivirals; and released high-level animal model summary tables on the NCATS OpenData Portal on June 29.

Animal Model Summaries

Animal model summary tables provide guidance on therapeutic type and present observed characteristics for small animal and nonhuman primate (NHP) models. The Preclinical WG is now creating detailed “Product Sheets” on each model to be released onto the OpenData Portal soon and is working to develop a mechanism for maintaining these summaries as more animal model testing data are generated.

Viral Reference Strain

The Preclinical WG is reconsidering its initial selection of the Washington Strain for use as a SARS-CoV-2 reference strain because of reports of other strains becoming the dominant infectious agent. The WG is considering a reference viral strain containing the D164G mutation (the dominant strain now circulating) and has contacted BEI, the current supplier. To increase production capacity and understand genetic variation during the production process, SOPs and consistent batch release requirements are being generated under Dr. Clint Florence’s leadership (NIAID). Once standards are finalized, ACTIV will discuss secondary production with (b) (4) are currently under consideration).

Discussion

Dr. Collins asked about the feasibility of selecting two viral reference strains (e.g., one with the D164G polymorphism and one without). Dr. Young acknowledged the need to adapt quickly to the changing SARS-CoV-2 landscape, and conveyed the Preclinical WG’s strategy to select one main reference strain (the dominant strain in circulation) and then to validate results from that main reference using a panel of geographic isolates representing SARS-CoV-2’s genetic diversity across global regions. Dr. Young also acknowledged the potential value of selecting two primary reference strains but cautioned that this approach may introduce unworkable complexity (e.g., by doubling the number of samples required for high-throughput screening).

Therapeutics-Clinical WG

Eric Hughes, MD, PhD, Novartis; Sarah Read, MD, NIAID

TX-Clinical WG Co-Chairs provided updates on the activities of its Master Protocol and Agent Prioritization Subgroups (MPSG and APSG, respectively).

Master Protocol Subgroup

The MPSG has completed development of and established governing bodies for ACTIV-1, ACTIV-2, and ACTIV-3 master protocols, and has submitted the protocols to FDA for Pre-IND or IND review. Summary information on these protocols, as well as on ACTIV-4 (being led by the National Heart, Lung, and Blood Institute [NHLBI]) are below:

- **ACTIV-1:** (phase III; immunomodulators; inpatients; Pre-IND submitted; August launch)
 - Sponsor: NCATS Trial Innovation Network (TIN) + CRO
- **ACTIV-2:** (phase II/III; neutralizing monoclonal antibodies [mAbs]/antivirals; outpatients; IND submitted; July launch)
 - Sponsor: NIAID AIDS Clinical Trials Group (ACTG) + CRO
- **ACTIV-3:** (phase II/III; neutralizing mAbs; inpatients; Pre-IND submitted; July launch)
 - Sponsor: NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO
 - ACTIV-3 will include phase I testing option for agents that need it
- **ACTIV-4:** (phase III; anticoagulants; outpatient, inpatient, and prophylaxis; protocol in development; July launch)
 - Sponsor: NHLBI-NINDS Network of Networks

The MPSG is now coordinating with lead networks, agencies, company partners, and/or CROs to plan and execute protocol implementation for ACTIV-1, -2, and -3, and is transitioning main operations of all ACTIV master protocols to NIH and Operation Warp Speed (OWS). It will also facilitate appropriate governance for all master protocols and has already convened the Agent Selection Committee (ASC) and Trial Oversight Committee (TOC), as well as Protocol Leadership Committees, for both ACTIV-2 and -3 (which also share a data safety monitoring board [DSMB]). The ASC has already developed recommendations for two neutralizing mAbs that the TOC will review for approval on July 2, 2020. The ASC will continue to recommend mAbs for TOC review each week. (b) (4) in review, and several other companies have expressed interest in providing mAbs for potential ACTIV-2/-3 testing.

Agent Prioritization Subgroup

The APSG continues to collect data on agents of interest and to sort the agents into classes: (1) antivirals, (2) host-targeted/immunomodulators, (3) symptomatic/supportive therapies, and (4) neutralizing mAbs. It has refined its prioritization strategy and agent scoring criteria for Wave 2 (criteria are weighted differently across agent classes; mAbs must meet minimum entry criteria to be considered for testing) and is completing triage and scoring of the 12 candidate antivirals submitted through ACTIV's Compound Survey. Unlike Wave 1, Wave 2 is considering agents earlier in the development pipeline (e.g., agents with no existing clinical data), so preclinical

validation is of increased importance, and the Subgroup's revised triage process reflects this shift by requiring multiple ascending dose studies, safety data to support 14-day exposure, and other information.

Discussion

Dr. Read confirmed that all ACTIV master protocols incorporate placebo comparators and that agreements are in place for agent sponsors to provide sufficient placebo supplies for each trial.

Clinical Trial Capacity WG

Elizabeth Desrosiers, MS, PMP, Merck; Michael Kurilla, MD, PhD, NCATS

The CTC WG Co-Chairs provided updates on the activities related to clinical trial capacity and innovations inventories. The CTC WG has thus far received survey responses from 54 networks, 679 sites, and 39 CROs or SMOs. These survey data are compiled into a Tableau-based geo-tracking dashboard that supports queries and presentations through a comprehensive view. The dashboard overlays current geographic COVID-19 case and death data (7-day moving average) or COVID-19 predictive data with site locations globally, which, combined with clinical trial capacity survey data, may be used to optimize therapeutics and vaccine trial network, site, and/or CRO/SMO selections. The CTC WG consults with the ACTIV-2 and ACTIV-3 operations teams on trial site innovations that may help to support execution of the protocols and expects to finalize its Home Nursing playbook by July 3. Further innovations playbooks are also being planned, focusing on electronic clinical outcome assessment [eCOA]/"bring your own device" [BYOD], eConsent, remote monitoring, and site training/tools. Playbooks will have a common structure and may be made available through the dashboard.

CTC Dashboard Access: Defining "ACTIV Involvement"

The CTC WG asked survey respondents whether or not their responses could be made accessible to ACTIV. The EC has since agreed to define individuals as "involved" in ACTIV if they are (1) staff working on COVID-related efforts at companies that are ACTIV Leadership members with the intent of public health benefit and/or to eliminate duplication of efforts; (2) individuals working on the development and/or execution of ACTIV-branded clinical trials; or (3) staff involved in COVID-related efforts at organizations coordinating and/or aligning with ACTIV for public health benefit and/or to eliminate duplication of efforts.

Discussion

Dr. Kurilla confirmed that additional geographic case data can be added to the CTC dashboard as needed to help track and predict patterns of infection and match trials to areas/populations of interest. Dr. William Pao suggested adding geographic mappings of viral genetic data to the dashboard to help track which viral strains are being detected and tested in different regions.

Vaccines WG

Douglas Lowy, MD, National Cancer Institute (NCI)

In addition to its CHIM publication being released today, the Vaccines WG is now refining a second manuscript reviewing existing evidence on vaccine-associated enhanced disease and concluding that there is no basis for prescribing/proscribing vaccine design based on prior experience with vaccines or natural infection. Vaccine-associated enhanced disease, if it happens, may be identified through safety and efficacy monitoring of clinical trials or pharmacovigilance. The manuscript will be submitted to a journal in approximately 2 weeks.

The Vaccines WG also continues to support development of harmonized vaccines efficacy trials. It has provided NIAID with input regarding the DSMB membership and charter for COVID-19 Prevention Network vaccine trials; reviewed the value of, and potential power for, analysis of secondary endpoints in these trials; and has been reviewing resources/plans for community engagement. Dr. Lowy highlighted that COVID-19 disease burden and outcome disparities are concentrated in subpopulations (e.g., patients aged 60 and above, patients with preexisting conditions, and patients of color). He asked Leadership Team members to consider the implications of these disparities for clinical trial representation and recruitment, posing three specific questions:

1. What representations of populations are important for the primary and final analyses?
2. What, if any, tradeoffs in recruitment speed are justified to increase representation of specially affected subpopulations?
3. How can ACTIV Leadership help to accelerate recruitment of important subpopulations?

Discussion

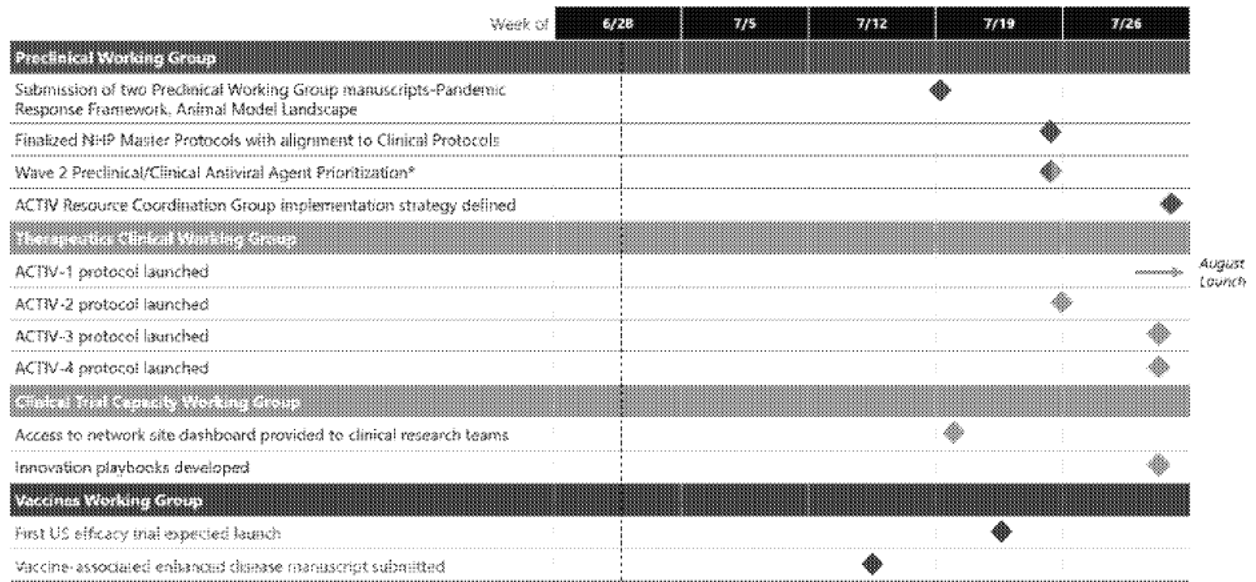
Dr. Lowy noted that the vaccine developers in the Vaccines WG have confirmed that they aim to enroll patients from important subpopulations in their vaccine trials. Drs. Anthony Fauci and Larry Corey highlighted the need to coordinate across vaccine testing efforts and to engage community representatives from important subpopulations to ensure both that vaccine candidates are tested within these populations and that these populations then have access to any effective vaccines. Dr. Collins stressed that diversity of participation in vaccine trials is of utmost importance and will require “all hands on deck” to gain confidence of, and successfully recruit, subpopulations of interest. Dr. Janet Woodcock noted that OWS and the TX-Clinical WG are now establishing community advisory boards (CABs) that could help to ensure adequate subpopulation recruitment for therapeutic trials. Dr. Corey invited participants in the meeting for recommendations of resources or contacts for outreach to underserved communities to support COVID-19 clinical trials. [These recommendations can be sent to Dr. Corey or Dr. Michael Santos (b) (6)]

July Milestones and Discussion

Mr. David Wholley presented the below graphic picturing planned ACTIV milestones for July:

ACTIV Leadership Team Meeting

July 1, 2020



We Are Here

Appendix A: Participants List

Francis Collins, MD, PhD, Director, National Institutes of Health (NIH) (Session Co-Leader)

Paul Stoffels, MD, Vice Chairman of the Executive Committee and Chief Scientific Officer, Johnson & Johnson (Session Co-Leader)

Christopher P. Austin, MD, Director, NCATS, NIH

Kara Carter, PhD, Executive VP Infectious Disease, Evotec

Carlos Castillejos, MD, PhD, Vice President External Affairs Science & Medicine at Johnson & Johnson

Marco Cavaleri, Head of Office, Anti-infectives and Vaccines, EMA

Tomas Cihlar, PhD, VP of Virology, Gilead Sciences

Christine Colvis, PhD, Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH

Larry Corey, MD, President and Director Emeritus, Fred Hutchison Cancer Research Center

Michelle Culp, MPH, Office of the Director, NIH

Gary Disbrow, PhD, Director, Division of CBRN Countermeasures, HHS and Acting Director, BARDA

Elizabeth Desrosiers, MS, PMP, Executive Director, Clinical Sciences and Study Management, Merck

Mikael Dolsten, MD, PhD, CSO and President, Worldwide R & D, Pfizer

Anthony Fauci, MD, Director, NIAID, NIH

Maria Freire, PhD, President and Executive Director, FNIH

Ellen Gadbois, PhD, Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy

Jordan Gladman, PhD, Health Program Specialist, NIH

Thomas J. Hudson, MD, Vice President of Oncology Discovery and Early Development, AbbVie

Eric Hughes, MD, PhD, Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis

Michael Kurilla, MD, PhD, Director, Division of Clinical Innovation, NCATS, NIH

H. Clifford Lane, MD, Deputy Director for Clinical Research and Special Projects, NIAID

John Lepore, MD, SVP, R&D Pipeline, GlaxoSmithKline (GSK)

Douglas Lowy, MD, Principal Deputy Director, National Cancer Institute (NCI), NIH

Raburn Mallory, MD, Senior Director, Clinical Development Infectious Disease & Vaccines, MedImmune

Peter Marks, PhD, Director, Center for Biologics Evaluation and Research, FDA

Hilary D. Marston, MD, MPH, Medical Officer/Policy Advisor, NIAID, NIH

David Meeker, MD, KSQ Therapeutics (formerly Genzyme)

Renate Myles, Deputy Director for Public Affairs, Office of Communications and Public Liaison, NIH

Ajay Nirula, MD, Vice President, Immunology, Eli Lilly

William Pao, PhD, MD, Head, Pharma Research & Early Development, Roche/Genentech

Ashley Parker, PhD, Health Science Policy Analyst, NIH

Roger M. Perlmutter, MD, PhD, EVP and President, Merck Research Laboratories

Robert M. Plenge, MD, PhD, SVP, Research & Early Development and Head, Immunology, Cardiovascular, Fibrosis, and Global Health Thematic Research Center, Bristol-Myers Squibb

Andrew S. Plump, MD, PhD, President, Research and Development, Takeda

Rachel B. Ramoni, DMD, ScD, Chief Research and Development Officer, Department of Veterans Affairs

Sarah Read, MD, Deputy Director, Division of AIDS, NIAID, NIH

John C. Reed, MD, PhD, Executive Vice President, Global Head of Research & Development, Sanofi

Doris J. Rouse, PhD, VP, Global Health Technologies, RTI International

Daniel M. Skovronsky, MD, PhD, Senior Vice President and Chief Scientific Officer, Eli Lilly and Co.

Peter Stein, MD, Director, Office of New Drugs, FDA

Lawrence Tabak, DDS, PhD, Principal Deputy Director, NIH

John Tsai, MD, Head, Global Drug Development and CMO, Novartis

Herbert (Skip) Virgin, MD, PhD, EVP Research and CSO, Vir Biotechnology

Janet Woodcock, MD, Director, Center for Drug Evaluation and Research (CDER), FDA; Operation Warp Speed

John Young, PhD, Global Head, Infectious Diseases, Roche

John T. Burklow, Associate Director for Communications and Public Liaison, NIH

Gary H. Gibbons, MD, Director, NHLBI, NIH

Adrienne Hallett, Associate Director for Legislative Policy and Analysis, NIH

Carrie D. Wolinetz, PhD, Associate Director for Science Policy, NIH

Stacey Adam, PhD, Director, Foundation for the NIH (FNIH)

Greta Gorman, Director of Communications, FNIH

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Abbey Meltzer, MPS, Vice President of Communications and Events, FNIH

Joseph P. Menetski, PhD, Associate VP of Research Partnerships, FNIH

Michael Santos, PhD, Associate VP of Science, FNIH

Karen Tountas, PhD, Scientific Program Manager, FNIH

David Wholley, MPhil, Senior VP of Research Partnerships, FNIH

Margaret Anderson, Managing Director, Deloitte

Nina Gonzalez, Senior Manager, Deloitte

Benjamin Stratton, Manager, Deloitte

Brett Tolman, MA, *Manager, Deloitte*

Jonathan Wachtel, *Manager, Deloitte*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

Rosa Maria Alvarez, *Senior Consultant, Deloitte*

Olivia Elsaid, *Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Additional notes from the Zoom Chat Transcript (not directly addressed in the meeting)

14:28:24 **From Larry Corey:** I am serious that from my colleagues in industry that if you have board members / resources who have contact with communication companies / forums that understand these underserved communities, I would be interested in speaking to them.

14:29:08 **From Rachel Ramoni:** All of Us has done a great job of reaching out to underserved populations.

14:29:41 **From Rachel Ramoni:** We in VA of course have a large community of underrepresented people (mostly men, though).

14:30:23 **From Gary Gibbons:** ACTIV has several high-profile papers of the strategy so PPP leadership might consider a special/specific piece that addresses ACTIV commitment to inclusion-diversity.

14:30:56 **From Larry Corey:** Thanks Rachel, we have been talking to them quite frequently. Appreciate your help

High-Level Meeting Summary

The Executive Committee (EC) of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership met with Co-Chairs of all four ACTIV Working Groups (WGs) to receive updates on the status of ACTIV trial recruitment, assess the status of EC action items from previous meetings, review progress toward fulfilling each WG's respective remits, and discuss ACTIV milestones and future plans. The Preclinical WG provided updates on SARS-CoV-2 viral reference strains to be used in ACTIV preclinical testing and on strategies for obtaining any data needed to support ACTIV agent prioritization; the Therapeutics-Clinical (TX-Clinical) WG reviewed the progress of its master protocol development and launch efforts and of its Wave 2 agent prioritization activities; the Clinical Trial Capacity (CTC) WG described its closing activities as it approaches its sunset on July 31, 2020; and the Vaccines WG reported on its discussions of various issues, including vaccine-associated enhanced disease, live vaccines that could be used to induce nonspecific immunity, study of vaccine efficacy in pregnant women, and implications of first licensure of an effective vaccine for other vaccine trials.

New Action Items from this Meeting

Action	Owner
1. Add criteria that clearly includes a virus that harbors a new mutation predicted to make a vaccine unresponsive as consideration for potential reference strain.	Preclinical Working Group
2. Develop a proposal for resourcing needs to maintain the Innovation Playbooks after the CTC Working Group sunsets	Clinical Trial Capacity Working Group
3. Gary Gibbons and Andy Plump will follow-up regarding access to natural history studies using available EHR data	Andy Plump, Gary Gibbons

Progress on Ongoing Action Items from Previous Meetings

The EC received updates on the status of ongoing action items from previous meetings, which are summarized in the table below. Additional participant comments on specific action items are summarized beneath the table.

	Action	Owner	Date Initiated	Progress Notes
1	ACTIV Leadership Team private sector members are asked to recommend resources to support outreach to underserved communities for COVID-19 clinical trials and send to Michael Santos (b) (6)	ACTIV Leadership Team Members	7/1 Leadership Team Meeting	At least two organizations (Roche and Merck) have reached out to offer their expert resources
2	Evaluate potential for natural history studies and connect Gary Gibbons with the appropriate COVID-19 (b) (4)	(b) (6)	7/1 Leadership Team Meeting	In Process – update today
3	Develop a plan to produce viral strains that can be used for Preclinical testing and follow-up with (b) (4)	ACTIV Preclinical Working Group	6/17 Executive Committee Meeting	Follow-up complete – implementation plan under way
4	Consider further the request to establish a potential additional ACTIV workstream to create a centralized data warehouse/cloud infrastructure for sharing clinical trials and real-world evidence data on COVID; or whether simply to partner with other initiatives in this area	Francis Collins, NIH; Michelle Culp, COVID-19 R&D Consortium	6/17 Executive Committee Meeting	In Process
5	Set metrics related to cycle times and benchmarks for improvement in order to accelerate the preclinical space	Preclinical Working Group	6/3 Leadership Team Meeting	Metrics were added to the Preclinical Working Group manuscript currently in preparation, with planned submission week of July 20

Regarding action item 2, Dr. Gary Gibbons reported that various strategies are being assessed to help track individual patients longitudinally using (b) (4). He noted that NIH is also exploring ways to leverage control groups' electronic health record (EHR) data to conduct long-term follow ups, as well as to generate patient registries using NIH clinical sites. Dr. (b) (6) noted that (b) (4).

Update on ACTIV Trial Recruitment

Dr. Francis Collins provided updates on efforts to identify and enroll (and perhaps oversample) diverse participants in both ACTIV and Operation Warp Speed (OWS) therapeutic and vaccine trials. These efforts are key to ensuring that COVID-19 therapeutics and vaccines are evaluated in populations (e.g., African Americans and older Americans) that have been disproportionately affected by the disease. In the immediate future, NIH leadership aims to ensure that the CRO running two-thirds of sites in the upcoming Moderna trial, which is scheduled to begin patient enrollment on July 27, follows an effective strategy for recruiting diverse participants (the remaining one-third of sites will be run by NIAID).

On July 4, NIH leadership discussed current strategies to enroll high-risk populations with representatives of the NIAID COVID-19 Prevention Trials Network (CoVPN) and the ACTIV Vaccines WG. Then, on July 10, the NIH/ACTIV/CoVPN team met with (b) (4) to discuss collaborative opportunities to enroll patients from high-risk populations. They created a matrix to help identify geographical overlap between available sites and existing community engagement efforts to help support enrollment of populations of interest.

In addition, to help prepare for other forthcoming trials that will require enrollment of subjects from high-risk populations, Dr. Collins appointed both Dr. Gibbons and Dr. Eliseo Perez-Stable, Director of the National Institute on Minority Health and Health Disparities (NIMHD), to direct a new NIH Community Engagement WG, which will assist in all these recruitment efforts moving forward. Other NIH community engagement efforts, including those associated with the NCATS

CTSA's and with the All of Us study, could also be integrated into these efforts as appropriate, as could the Health Resources and Services Administration's Federally Qualified Health Centers.

Dr. Collins is also contacting members of the Congressional Black Caucus and the Congressional Hispanic Caucus to solicit members' willingness to issue announcements of ACTIV/OWS trials to their constituents as part of a public relations campaign to stimulate recruitment of minority patients.

Preclinical WG Updates

Since the last Leadership Team meeting, the Preclinical WG has harmonized the contents and figures for its draft Animal Model and Pandemic Response Drug Development SOP manuscripts and has discussed ways to systematically identify and prioritize combination therapies to rapidly enter clinical testing. The WG has also continued earlier discussions about (1) selecting and producing reference SARS-CoV-2 strains for use in ACTIV preclinical studies and (2) linking researchers with the resources and expertise they need to generate preclinical data for agent prioritization.

SARS-CoV-2 Reference Strains

The WG recommends using both the Washington and the D614G strains as references to help support bridging studies (previous studies generated data using the Washington strain, but D614G has emerged as the dominant strain and is now being more widely studied), as well as to help establish a panel of five to ten global strains against which promising agents can be tested. Previously, EC members expressed concern about potentially limited production capacity for viral reference strains. However, BEI has confirmed that it will upgrade its equipment to produce 20L of reference viral strain every 2 weeks starting in August. BEI will serve as a primary production site; Bioqual and SRI will serve as secondary production facilities if necessary.

Considering the potential for continuous viral mutation, the Preclinical WG has also drafted the below criteria for evaluating newly emerging strains for consideration as additional references:

- Observed changes in regional population dominance of infectious activity (>80% of new cases are the "new" strain)
- Dramatic change in disease presentation in humans (e.g., new symptoms or mortality rates)
- Clinically confirmed evidence of viral resistance to front-line antiviral therapy
- Clinic or NHP evidence of increased antibody-induced disease enhancement
- Loss of neutralizing capacity of a panel of monoclonal and polyclonal antibodies against the current reference strain (e.g., loss of >10% neutralizing capacity or significant alterations in major neutralizing epitopes consistent with immune escape)
- Significant increase in replication capacity (in vitro-determined ID₅₀ greater than a log change from current reference)
- Viral stability changes in vitro (if the new strain is significantly more variable than the current strain)

These criteria generally focus on changes in observed clinical characteristics (either in patients or in samples obtained during patient follow-up) and will be refined through consultation with infectious disease epidemiologists.

Obtaining Preclinical Data Needed for Agent Prioritization

The Preclinical WG is creating a match-making process by which researchers developing agents against SARS-CoV-2 can identify and leverage the resources they need to generate all preclinical data required to support ACTIV agent prioritization (e.g., resources such as BSL 3/4 and screening facilities). The WG is working jointly with the TX-Clinical WG and a group of external experts to assess agents that were deferred during its antiviral prioritization process for lack of preclinical data and to craft a process to help companies or academic labs connect to whatever resources they need to generate data required for ACTIV testing.

Discussion

Regarding the WG's criteria for considering potential future additions of reference strains, Dr. Collins recommended adding any strain that harbors a new mutation that would predict vaccine unresponsiveness; the Preclinical WG will add this consideration to its list of criteria. Regarding the establishment of a global representative panel of SARS-CoV-2 reference strains, Dr. Andrew Plump suggested that this panel include remdesivir-resistant strains, potentially including those developed in vitro to screen next generation agents.

Dr. Plump also highlighted recent evidence suggesting that type I interferon (IFN) response is muted in infected patients and suggested that ACTIV consider repurposing immune-oncology agents that activate IFN response. Dr. Young agreed that this approach deserves consideration, but also highlighted the need to appropriately time IFN response to avoid exacerbating disease.

Dr. William Pao asked how tolerability was evaluated during antiviral agent prioritization, and Dr. Sarah Read explained that it was considered as a component of the *safety* scoring criterion. The agent prioritization team scored each agent as either "go" or "no go" based on whether its existing data suggested "major safety concerns."

Therapeutics-Clinical WG Update

TX-Clinical WG Co-Chairs presented updates on the WG's master protocol development and agent prioritization efforts.

Master Protocol Development

The Master Protocol Subgroup (MPSG) has completed development of ACTIV-1, ACTIV-2, ACTIV-3 and ACTIV-4, all of which are undergoing FDA review (either Pre-IND or IND applications or DSMB review). It has also established governance bodies for all its master protocols and transitioned main protocol operations to NIH and OWS. Its next steps are to coordinate with each protocol's lead networks, agencies, company partners, and CROs to plan and execute protocol implementation. Summary information on the status of each of the MPSG's master protocols is below:

- **ACTIV-1:** (phase III; immunomodulators; inpatients; Pre-IND submitted; August launch)
 - Sponsor: Duke Clinical Research Institute (DCRI) + NCATS Trial Innovation Network (TIN) + CRO
 - First agents tested will be: (b) (4)
- **ACTIV-2:** (phase II/III; neutralizing monoclonal antibodies [mAbs] and oral antivirals; outpatients; IND submitted; preparing community outreach campaign to encourage patient enrollment in outpatient trial; preparing sites and database for July launch)
 - Sponsor: NIAID AIDS Clinical Trials Group (ACTG) + CRO
 - First agents tested will be: Eli Lilly's mAb and Ridgeback/Merck's EIDD-2801/MK-4482
- **ACTIV-3:** (phase II/III; neutralizing mAbs; inpatients; IND submitted; preparing sites and database for July launch)
 - Sponsor: NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO
 - ACTIV-3 will include phase I testing option for agents that need it
 - First agent tested will be: Eli Lilly's mAb
- **ACTIV-4:** (phase III; anticoagulants; inpatients; protocol to go to DSMB for final approval on July 17; preparing sites for July launch)
 - Sponsor: NHLBI-NINDS "Network of Networks"

Regarding the community outreach campaign being developed for ACTIV-2, the MPSG has been working with PPD (a CRO) to establish patient-centered websites and materials to distribute to prospective patients providing them with information and instructions on how to enroll. It has also been working with the public relations firm Klick Communications to establish a "directed media presence" on platforms such as Google and Facebook so that information on ACTIV-2 will rise to the top of results for relevant online searches (e.g., for "COVID-19 treatment trials"). The community outreach campaign also involves direct contacts with key stakeholder groups such as AARP, workers unions, and employee groups in high-risk settings, as well as links with COVID-19 diagnostic centers (e.g., through RADx-UP) to enroll newly diagnosed patients.

Agent Prioritization

The Agent Prioritization Subgroup (APSG) has defined its strategy and approach for Wave 2 agent prioritization and has conducted Wave 2 evaluations of antivirals, immunomodulators, and neutralizing monoclonal antibodies (mAbs). Its next steps are to continue to evaluate and prioritize immunomodulators, antivirals, and symptomatic/supportive therapies during Wave 2 evaluation, and to facilitate selection and entrance of neutralizing Abs to both ACTIV-2 and ACTIV-3 trials.

Drs. (b) (6) showed detailed tables demonstrating (b) (5)

General status updates of agent prioritization efforts are summarized below.

Neutralizing mAbs

The ACTIV-2/-3 Agent Selection Committee has evaluated seven neutralizing Abs, and the Trial Oversight Committee (TOC) has approved three of the seven agents to advance for clinical trial planning by the ACTIV-2/3 teams (from (b) (4)); however, approvals are contingent on positive readouts from Phase I testing.

Antivirals

In collaboration with the Preclinical WG and OWS, the Antivirals Subteam has completed Wave 2 assessment of 23 antivirals. The Agent Prioritization Committee has reviewed the Subteam's recommendations, the TOC has (b) (4) for testing in ACTIV-2, and the ACTIV-2 team is now working with (b) (4) to incorporate the agent into the protocol. Two other agents are still being considered (b) (4) eight agents were deferred to future review rounds, and 12 agents were classified as "no go."

Immune Modulators

In collaboration with the Preclinical WG, the Immune Modulators Subteam is executing Wave 2 agent prioritization. It is currently evaluating 11 candidates and will soon begin a second round of evaluation for a new batch of agents.

Symptomatic/Supportive Therapies

The APSG continues to collect candidate submissions via the ACTIV Compound Survey and will establish a Symptomatic/Supportive Therapies Subteam to evaluate and prioritize these agents.

Discussion

Dr. (b) (6) asked how reports (b) (5) to include it in ACTIV-2 trials. Dr. Hughes acknowledged that further work is needed to establish the compound's in vitro activity and safety profile before it can enter clinical testing.

Dr. Gibbons asked whether the TX-Clinical WG had considered potential therapeutic targets at the intersection of inflammation and thrombosis. WG Co-Chairs noted that Wave 2 prioritization of symptomatic/supportive therapies (e.g., antithrombotics) is expected to begin soon.

Dr. Plump asked whether the TX-Clinical WG and FDA had encountered any challenges in moving agents through the agency's review process, given the volume of work involved in anti-COVID-19 efforts. Dr. Read noted that she would need to poll members of the WG for more details but stated that the TX-Clinical WG's FDA representative has provided valuable input and facilitated crucial connections between WG members and FDA personnel to accelerate timelines; timelines have certainly been faster than before the pandemic began. Dr. (b) (6) FDA suggested that (b) (5)

Dr. Marks encouraged participants to escalate any concerns about specific high-priority products lagging during review stages so that they can be rapidly addressed. Dr. Plump will

follow up with selected ACTIV Leadership Team members offline to solicit potential process improvements to help accelerate review cycle timelines.

Clinical Trial Capacity WG

The CTC WG has thus far received survey responses from 54 networks, 707 sites, and 39 CROs or SMOs. These survey data are compiled into a Tableau-based dashboard created to query and present survey data, and to overlay it geographically with case and death data at the country level globally, and predictive data at the county level in the U.S.. The WG has also determined that the Protect platform contains up-to-date status reporting from state health departments and hospitals (i.e., number of cases and deaths, hospital utilization metrics, and reported COVID-like and Influenza-like illness counts); the data from this platform will be added to the Tableau dashboard by the end of July pending data transfer. The WG expects to complete creation of capacity surveys versions 2.0 by the end of July but will not launch until Fall 2020 to help reduce “survey fatigue” among respondents. The WG is also working to seamlessly transfer the dashboard tool to NCATS by July 31 so that NCATS can maintain it long term. NCATS is negotiating an extension of the license agreement with Tableau, which currently ends August 1.

The CTC WG has also consulted with both the ACTIV-2 and ACTIV-3 teams to identify trial site innovations that can support each protocol. The WG has finalized two of its Innovations Playbooks focused on Home/Mobile Nursing and eConsent and is developing three more that will focus on eCOA/BYOD/Hybrid, Remote Monitoring, and Site Training/Tools. Each of these Playbooks contains instructions for its use, descriptions of services covered, and lists of potential vendors to provide services, as well as guidance documents from relevant government agencies. The Playbooks will be made broadly available to ACTIV and hosting the playbooks long-term on the dashboard is being explored.

The CTC WG will have fulfilled its remit by the end of July and will discontinue its activities at that time. The WG is drafting a plan to maintain and refresh its Innovations Playbooks after this month.

Vaccines WG

The Vaccines WG discussed Dr. (b) (6) suggestion of (b) (4) to stimulate nonspecific immunity to prevent COVID-19. Dr. (b) (6) presented existing evidence in support of this idea to the Vaccines WG on July 13, and proposed two potential approaches to testing the effectiveness of this strategy: (1) randomized controlled trials (which may be too costly); and (2) influenza challenge studies (to establish proof-of-principle of non-specific immunity and investigate mechanisms). Further discussion is needed to explore these possibilities.

The Vaccines WG has also discussed studying COVID-19 vaccine candidates in pregnant women. This would likely require bridging studies to ensure a sufficient sample size of pregnant patients to determine efficacy. The WG has also continued to refine its forthcoming manuscript reviewing evidence on vaccine-associated enhanced disease.

Implications for Licensure of First Successful Vaccine

The Vaccines WG has tried to assess the implications of the licensure of a first COVID-19 vaccine for *other* vaccine efficacy trials that are either ongoing or planned at the time of that licensure. The first vaccine with a successful primary analysis will likely receive Emergency Use Authorization and licensure. There will be guidance about priority populations for vaccination, and it remains unclear what the implications will be for ongoing placebo-controlled trials that include those populations; this issue requires further consideration. For those vaccines that have not yet begun clinical testing at the time of licensure of the first successful vaccine, placebo-controlled trials may be viewed as unethical, but randomized noninferiority efficacy trials may require infeasibly large samples. These issues will persist until the identification of correlates of protection sufficient for licensure of other vaccines, and thus it is important to shorten that interval as well as prepare to manage trials during that interval.

Discussion

Dr. (b) (4), (b) (6) stressed the challenges and complexities involved in identifying correlates for licensure across vaccines, particularly given the fast pace of development. Dr. (b) (4), (b) (6) noted that the first approved vaccine may require storage at very low temperatures, and thus may not be suitable for use in certain geographic regions; this may be an argument for continuing placebo-controlled trials of vaccines more suitable for those regions, at least in those regions.

Dr. (b) (4), (b) (6) asked whether (b) (4) —in addition to polio vaccines—have been considered as potential inducers of nonspecific immunity. Dr. (b) (4), (b) (6) confirmed that both of those options were discussed. Dr. (b) (4), (b) (6) noted that (b) (4) is currently under study in a clinical trial, but that its manufacturing process presents drawbacks to more widespread use.

ACTIV WG Future Plans

Mr. David Wholley presented the below table displaying anticipated activities for each WG after July:

ACTIV WORKING GROUP	FUTURE STATUS AS OF JULY 31, 2020	RECOMMENDED ACTION
Preclinical Working Group	- Initial infrastructure complete "Resource matching" will need to continue into the fall - Need to oversee preclinical testing/advancement of candidate therapeutics (if funding exists)	 Continue current operation
Therapeutics Clinical Working Group	- Continued prioritization of agents through August - Facilitate launch of trials through August - Support ongoing trial governance	 Continue current operation
Clinical Trial Capacity Working Group	- Geotracking Dashboard complete and transferred to NCATS - Innovations inventory and playbooks complete	Cease regular operations as of July 31 Key WG members will be available to advise NCATS on maintaining and updating tools as needed
Vaccines Working Group	- Input to harmonized vaccine trial designs complete - Manuscript on enhanced disease - Vaccine trial operations will be overseen by sponsors, NIAID and OWS	Cease regularly calendared meetings as of July 31 Reconvene as needed to address critical vaccine development issues

The EC generally endorsed the plans captured by the table above.

Adjourn

An ACTIV Leadership Team meeting will be scheduled for Wednesday July 29 at 2:30 pm ET.

Appendix A: Participants List

Francis Collins, MD, PhD, *Director, National Institutes of Health (NIH) (Session Leader; Executive Committee Co-Chair)*

Paul Stoffels, MD, *Vice Chairman of the Executive Committee and Chief Scientific Officer, Johnson & Johnson (Executive Committee Co-Chair)*

James Anderson, MD, PhD, *Senior Investigator, National Heart, Lung, and Blood Institute (NHLBI)*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Michelle Culp, MPH, *Office of the Director, NIH*

Elizabeth Desrosiers, MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

Gary Disbrow, PhD, *Acting Director, Biomedical Advanced Research and Development Authority (BARDA)*

Mikael Dolsten, MD, PhD, *CSO and President, Worldwide R & D, Pfizer*

Maria Freire, PhD, *President and Executive Director, FNIH*

Gary H. Gibbons, MD, *Director, NHLBI, NIH*

Adrienne Hallett, *Associate Director for Legislative Policy and Analysis, NIH*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

Michael Kurilla, MD, PhD, *Director, Division of Clinical Innovation, NCATS, NIH*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI)*

Renate Myles, *Deputy Director for Public Affairs, Office of Communications and Public Liaison, NIH*

William Pao, PhD, MD, *Head, Pharma Research & Early Development, Roche/Genentech*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Andrew S. Plump, MD, PhD, *President, Research and Development, Takeda*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH*

Lawrence Tabak, DDS, PhD, *Principal Deputy Director, NIH*

Carrie Wolinetz, PhD, *Associate Director for Science Policy, NIH*

Janet Woodcock, MD, *Director, Center for Drug Evaluation and Research (CDER), FDA*

John Young, PhD, *Global Head, Infectious Diseases, Roche*

Stacey Adam, PhD, *Director, Foundation for the NIH (FNIH)*

Stephanie James, PhD, *Senior VP of Science, FNIH*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate VP of Science, FNIH*

Karen Tountas, PhD, *Scientific Program Manager, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Margaret Anderson, *Managing Director, Deloitte*

Nina Gonzalez, *Senior Manager, Deloitte*

Benjamin Stratton, *Manager, Deloitte*

Brett Tolman, MA, *Manager, Deloitte*

Rosa Maria Alvarez, *Senior Consultant, Deloitte*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

Olivia Elsaid, *Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

SUMMARY OF DISCUSSION ON STEPS TO DIAGNOSE AND ADDRESS ISSUES WITH ACTIV-2 AND -3 TRIAL ACCRUAL – 8/28/20

Participants: Jim Neaton (U. Minn.), Manizhe Payton (NIAID), Sarah Read (NIAID), Sam Bozzelle (NCATS), Sam Jonson (NCATS), Laura McNay (NIAID), Davey Smith (UCSD), Kevin Bugin (OWS), Bill Erhardt (OWS), Stacey Adam (FNIH), Karen Tountas (FNIH), David Wholley (FNIH), Helen Chen (Deloitte), Jonathan Wachtel (Deloitte)

PROBLEM:

1. We have a number of problems with pushing out the proposed (b) (5) prepared by (b) (4); it is surely somewhat informative, but limited: for example the ACTIV (b) (5) for example is more current and in some cases more detailed. The group is not sure that competition from other studies is the main issue anyway (see below)—and therefore whether (b) (5) is even that useful for improving trial enrollment.
2. An additional problem with conducting an (b) (5) even with the (b) (5) is that there are multiple (b) (5) sites involved in COVID-19 studies. To whom should (b) (5) be addressed?
3. There is also (b) (5) many sites. In addition to the (b) (5) (b) (5) fairly extensively by NIAID, PPD, and other CROs. We need a more personal touch if outreach is to succeed. Investigator meetings offer one avenue, although individuals often share more insight when given the option to discuss matters one on one, and beleaguered site personnel may be more receptive to a phone call than a broadcast survey by email.
4. And, overall, the (b) (5) needs to be perceived from the get-go not as a request for information for its own sake, or a platform for deciding what other sites to open, but as an integral part of an offer for help: what are your key challenges, so we know how best to help you?
5. In fact, the main problem is not what other trials are open at most of the sites, really, but staffing. Sites need extra hands. Hospitals are simply not hiring because of financial concerns related to COVID-19. Even if funds were available, building a staff now (in a suitable timeframe) is very difficult. (b) (5)
6. The most productive sites have (b) (5) We should be asking more about what resources a site has put in or is willing to put into a trial than what other trials they have going on.
7. Furthermore, there is some (b) (5) sites that do not have a lot of competing trials, as they tend to also have less experience in conducting these trials.
8. (b) (5)
9. For (b) (5) in particular a related challenge is the frank lack of interest in the protocol. Part of this is related to the fact that staff have their hands full as already noted above, part to the difficulties of getting infusions done; but a lot has to do with a public perception that people who have contracted COVID should simply stay home, and not come into the hospital unless they absolutely have to. We need a major public communications effort that emphasizes that

participating in these trials is vital to defeating the virus, and is in the broad interest of the public health.

10. A few additional notes/caveats on such a (b) (5) [redacted]; since COVID-19 is a global pandemic and a good number of our sites are outside the U.S. Although we might be able to use the ACTIV protocols as an example of the kind of studies in which people should participate (as opposed to small, underpowered studies that are the norm), we need to (b) (5) [redacted] participate in COVID-19 trials, (b) (5) [redacted]

[redacted] Also, the central IRB (b) (5) [redacted] offers a good model. Finally, any such communication needs both a general public component (a PSA) and a targeted, (b) (5) [redacted]

PROPOSED SOLUTION AND ACTION ITEMS:

- 1) (b) (5) [redacted] (help, not information) to sites – Davey Smith and Manizhe Payton
- 2) (b) (5) [redacted] Davey, Manizhe) in the request and make sure it is reviewed (b) (5) [redacted] (Peter Kim, Laura McKay, Sarah Read)
- 3) (b) (5) [redacted]:
 - a. Can we get (b) (5) [redacted] set up? (Kevin Bugin/ David Wholley)
 - b. Can we (b) (5) [redacted] at investigator meetings? (see above – Peter, Laura, Sarah)
- 4) Public messaging:
 - a. Explore (b) (5) [redacted]
[redacted] inpatient and outpatient clinical trials (David W.)
 - b. Explore (b) (5) [redacted]
[redacted] (total of two meetings) for five minutes each (b) (5) [redacted]
[redacted] (David W.)

High-Level Meeting Summary

The Agent Prioritization Subgroup of the TX-Clinical Working Group (Sub-WG) reviewed the list of triaged agents and prioritized the assessment of those within the 'keep' and 'pending' categories in order to arrive at a list of agents to move forward for scoring.

A summary of key discussion points follows.

Triage Decisions

The Sub-WG reviewed the results of the first round of triage, which yielded three categories of agents: 'keep,' 'drop,' and 'pending' (b) (5). The discussion of the votes led to the following major decisions:

- (b) (4) was moved from 'keep' to 'drop' because this agent is involved in ongoing clinical trials; (b) (4) is mechanistically similar to (b) (4) and was thus moved to 'drop' as well.
- (b) (4) was moved from 'pending' to 'drop.'
- (b) (4) was moved to 'drop' because it is not currently FDA approved, but participants will reconsider this agent during the second wave of triage.
- (b) (4) was moved to 'drop' because this agent is not yet FDA approved.
- Participants decided to omit all (b) (4) because they are being studied robustly in ongoing clinical trials; however, (b) (4) will be kept in 'keep.'
- (b) (4) was moved to 'drop' because participants prioritized other antiviral agents (e.g., (b) (4)).
- (b) (4) was moved to 'drop' because the agent is currently being studied in a large clinical trial.

Discussion

Participants also discussed several potential gaps in the construction of the list as well as emerging data that may affect assessment of agents moving forward.

Dr. (b) (6) noted that only two of the twelve (b) (4) were merged into the current ACTIV Compound Inventory. Dr. (b) (6) will check whether an error was made in collating the list of agents or if the missing agents are slated for the second wave of review.

Participants noted that certain agents appear in the Inventory as duplicates under different compound formats. For example, (b) (4) are the same agent but (b) (4) is listed twice, once with a 'keep' and once with a 'drop' vote (b) (5).

Dr. (b) (6) recommended considering (b) (4) alone, because it has favorable (b) (4) alone.

He will share with Sub-WG members a recent (b) (4) treatment of SARS-CoV-2.

Dr. (b) (6) stressed the need to consider (b) (4) administration when reviewing this agent. Recent pathological studies of (b) (4) treatment of SARS-CoV-2 show that intratracheal administration may be required; intravenous delivery is not sufficient because microthrombi are not forming in blood vessels. Dr. (b) (6) will share these pathology reports with Sub-WG members.

Dr. (b) (6) will share the updated ACTIV Compound Inventory with the Preclinical WG to provide feedback.

Moving Agents to Scoring

The Sub-WG agreed that the (b) (5)

. Agents within each major class (b) (5)

will be assigned to members who have expressed a comfort scoring that class. All Sub-WG members will then collectively discuss the resulting scores and make final decisions to arrive at a set of prioritized compounds for clinical trials.

Next Steps

Dr. (b) (6) will share with Dr. (b) (6) a list of the remaining agents (b) (5) to arrive at a final recommendation.

Sub-WG members will notify Dr. (b) (6) which of the three agent categories they prefer to review, and Dr. (b) (6) will disseminate lists of agents according to those preferences. Sub-WG members will review their lists and utilize the scoring template to submit votes to Dr. (b) (6) by Friday, May 1 at 8:00 AM ET. Dr. (b) (6) will collate the votes and create a summary document to be discussed with Sub-WG members that afternoon; the goal of this Sub-WG is to provide ACTIV leadership with a final list of agents by Friday evening.

Appendix A: Participants List

SUBGROUP MEMBERS

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA) – Listening ONLY*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Walter Koroshetz, MD, *Director, National Institute of Neurological Disorders and Stroke*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Mike Vincent, MD, PhD, *Senior VP, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

Elizabeth Higgs, MD, *Global Health Science Advisor, Division of Clinical Research, NIAID*

INVITED PARTICIPANTS

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

Keith Gottesdiener, MD, *Chief Executive Officer, Rhythm Pharmaceuticals*

Elliott Levy, MD, SVP, *Global Development, Amgen*

Peter Wung, MD, MHS, *Associate VP, Global OMD Lead, Immuno-Inflammation, Sanofi*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Rosa Maria Alvarez, PhD, *Senior Consultant, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

ACTIV, Therapeutics-Clinical Master Prioritization Sub Group
Working Group Meeting 5, Key Takeaways

Wednesday, April 22st, 2020

Action Items

Action Items		
	Information	POC
1	Sarah Read to reach out to lead investigator in NIAID who should be engaged as Master Protocol Subgroup develops ACTT3. Add this to action items list and timeline	Sarah Read / Stacey Adam
2	Send ACTT2 to Working Group Members	Stacey Adam
3	Share Master Protocol design with Clinical Trial Capacity Working Group, Subgroup on Innovations to discuss potential innovations	Stacey Adam

Key Takeaways

- Master Protocol Subgroup reached consensus on three major elements (design, randomization, multiplicity) for the ACTT3 Amendment (“repurposed” Master Protocol). Drafting of “repurposed” Master Protocol to begin by April 24.
- An ACTT3 would be for those drugs are ready to go and in a phase of testing commensurate with ACTT1 and ACTT2, without any early phase clinical testing needed. For the *de novo* ACTIV Master Protocol, the early phase testing for compound efficacy screening would be built in with a more adaptive design.
 - In the “repurposed” protocol, WG will try to minimize changes and streamline ACTT3.
 - Group consensus that given the Therapeutics Clinical Working Group will not know the prioritized drugs until next week, the Master Protocol Subgroup should draft ACTT3 in a most expeditious way but understand some flexibility will be needed.
- Working Group reached consensus that we will not pursue a single arm study.
- Working Group reached consensus on Drug A:B:C vs Standard of Care (SOC). ACTT3 could be written with 3 drugs and a common SOC. We could leave the draft open to a 4th drug that can be adapted to placebo or another agent.
- ACTT3 will have a little adjustment for multiplicity. The primary focus will be A vs. SOC, B vs. SOC, and C vs. SOC.
- Master Protocol WG will plan for the worst that we may not be able to get any placebos but pursue placebos if possible.

Summary of Action Items List/Timeline Updates and ACTIV Leadership Meeting

- Overview of changes made to action items list and timeline: increased number of days needed for “selecting optimal structure and statistical design” and decreased number of days needed for “identifying top 2-5 repurposed drugs for initial draft of protocol.”
- Co-Chairs did not get a lot of questions from ACTIV leadership this morning. Our Working Group was given 10 minutes to present. There was not a lot of feedback.

Wednesday, April 22st, 2020

- Janet Woolcock did provide email comment strongly endorsing importance of a progressive trial with Bayesian adaptive measures and common SOC.
- From Director of Division of Microbiology and Infectious Diseases at NIAID: important to get buy-in from investigators who are part of ACTT now, so it doesn't seem like ACTIV is prescribing something to them and telling them to do it. Sarah Read to reach out to John B., investigator leading from within NIAID. Add this to timeline.
- WG will start with the "repurposed" protocol in our conversation today.

Defining understandings of "repurposed" and *de novo* Master Protocols, discussion around BET

- Need to confirm collective understanding of meaning of "repurposed" Master Protocol
- How far can we push away from the initial ACTT protocol without having the review process be too cumbersome? Can we push this all the way to a screening, short-turnaround trial, or does it need to be a trial with a larger patient population, etc.? How far can we "tweak" ACTT in ACTT3?
- There was a synopsis circulated with the WG for the BET trial, which is a screening protocol, platform study to look for big effects to then move into ACTT. It's not yet a study, and BET is not yet in place. It would be a separate, standalone protocol.
 - Suggestion that BET is a very different trial studying 50 people, exploratory, and doesn't seem to overlap with the ACTT.
- Proposal from WG member that whatever we do with ACTT3, we don't try to make it with "bells and whistles" in data and sample collection. Also, will likely not need Bayesian design since we view this as a short term measure before we start the *de novo* Master Protocol. We should keep it true to the ACTT1 and ACTT2 and study a few molecules reasonably well with a few tweaks. And then move forward quickly.
 - For the *de novo* Master Protocol, suggestion to think about it as being designed to really answer questions in an adaptive Bayesian to study many molecules as they come through, whether that means each arm has to be a little bigger, but when the trial is done, we'll get an answer that will meet as much as we need for regulators and give clear answers to doctors. But the approach for *de novo* would be to study a lot of compounds and result in something more everlasting.
 - Suggestion that something like BET still important. Propose that we think of BET as possibly feeding into either the *de novo* trial or into an ACTT3 type of confirmatory approach if and when the right time comes. BET will help figure out what the signals are and is more of a hypothesis testing.
- Subgroup members likes idea of not dramatically changing ACTT3, seems reasonable.
- Subgroup Chair commentary that the above is what we were trying to convey. An ACTT3 would be for those drugs were ready to go and are in a phase of testing commensurate with ACTT1 and ACTT2 without any screening needed. Then for the *de novo*, the screening would be built in with "Phase 2-3" learn/confirm/more adaptive design because we'd have more compounds in potentially earlier stages and different stages of testing.

Wednesday, April 22st, 2020

- In the repurposed protocol, we'll try to minimize changes (there will be some changes), but one of the changes is potentially not having daily data collection. We want to try and streamline ACTT3.
- In the *de novo* protocol, the drugs may come in as early as Phase 2, some Phase 3. We would have some sort of graduation criteria and that's where the flexible/adaptive designs would happen (going back to (b) (6) suggestion)
 - What's not addressed in either of these is the role of a BET, but it's addressed in terms of how we'd graduate. We could consider starting *de novo* further downstream so that a BET that had 50 drugs in it would've already gotten down to 20 drugs, and those 20 drugs would come into a *de novo* trial.
 - It's up to the WG to decide.
- Idea is that in ACTT3, we're ready to test just like ACTT1 is testing Remdesivir. The drugs would be ready to go in late Phase 2 or Phase 3, etc. Even though, we've decided not to use phases. Those drugs are ready to go, to be compared, and we just need to figure out what the comparison is to and where they will share controls, and a few of the "bells and whistles."
- *De novo* will be more adaptive because it starts earlier, and there's more fluidity in how much we have to learn and how much we're ready to verify that the drug works.
- One other expansion with *De novo* is that we're not going to restrict ourselves to hospitalized patients.
 - BET focuses on hospitalized. ACTT focuses on hospitalized. That would be another departure in the *de novo*.

Update on ACTT2 and Expeditious Approach to ACTT3

- From Co-Chair: ACTT2 has been redesigned to look a little bit more like a master protocol. It was most recently approved by FDA and better integrates ACTT1 and ACTT2. It reads more easily to accommodate additional agents, whereas before it was one protocol tacked on to the original.
- What would make (b) (5)) where we can say, for example, (b) (5)
- This would help protocol writing. We won't know the exact drugs, but we can focus on what we want to change in ACTT2 to go on to ACTT3. We can then go into endpoints, randomization, SoC, what can be shared, etc.
- Group consensus that if we don't know until next week what the prioritized drugs will be, we should draft ACTT3 in the way we want, in a most expeditious way.
- Question from WG about whether we will bring new sites on for ACTT3?
 - We need to sort this out. We don't know how many ACTT2 sites are opening that could do ACTT3. We should work with CTC WG, so we can plan out how to maximize efforts running simultaneously. We need to run a stable ACTT3 design with the CTC because they have a few innovations that they'd like to suggest, but they want to see what design we come up with first.
- Will there be new information about SOC coming out?

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- We may learn something on Monday from the ACTT1 readout. ACTT2 hasn't started yet and won't start before the DSMB meeting.
- Getting placebos for many of these drugs, particularly if we are putting more than 1-2 drugs into trial, will become limiting. For many commercial drugs, companies are not focusing on making placebos for them. There are solutions like over encapsulating, giving water, ascorbic acid – but we need to think about whether we are committed to a placebo control vs. Standard of Care control trials.

Group Decisions on Design, Multiplicity, and Randomization

- Group agrees that we will not pursue a single arm study.
- Suggestion to design study as a “placebo” control (aka a common drug with minimal beneficial effect, low safety risk profile) for now.
- If we can get a placebo, we'll take. If we can't get placebos, we can decide that we don't have time to over encapsulate, as this may add a few months.
- If we have 3 drugs, are we obligated to have 3 times the number of patients if it's a placebo comparator vs. a SOC comparator?
 - There's a cost to pay if you don't. You have to put many more patients on an ineffective comparator, and that in itself is undesirable.
 - It's not simply a matter of rapidly obtaining placebo for each agent but a question about tradeoff between efficiency and rigor.
 - Many drugs have different administration conditions- some are given once daily, some twice, injected, infused over an hour, etc. We should think about what we'll do in ACTT3.
 - If a SOC approach could work, how would we handle it?
- Even if we pool SOC, would we only pool for SOC that are concurrent in the randomization?
 - WG member suggestion not to pool across time because things can change so much.
- Getting back to the placebo issue, WG member preference would be to have a placebo group.
 - In the PREVAIL trial, it was difficult to not have a placebo. It was difficult on the staff to know they were giving no experimental treatment and watching people die.
 - Comment that that is a trial design and operational/psychological issue.
 - Comment that if you have 4 different arms, you could have 1 placebo arm with different placebos. If you have multiple arms, you may not have people getting everything at your site. It may be easier to mask that they're getting placebo. Can have 1 placebo be in pill form, one as an IV.
 - Important for some type of placebo.
 - SOC is changing rapidly, and people are getting better at managing patients. Need some way to control this.
- For now, we will assume that we'll write a protocol with A vs. B. vs. C vs. SOC. We'll assume that the ACTT3 protocol could be written with 3 drugs and a SOC. We'll leave it open for a 4th drug to come

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in or be easily adapted. We could start with 2 drugs and then later let 2 come in. We can write with that possibility to at least get us started with the protocol.

- WG member in favor of concurrent control.
- WG member – in terms of the placebo question, would prefer to do SOC. We need to be careful not to call this a placebo control trial. It's not really placebo-controlled or double-blind. We're doing this primarily because every patient gets something, and we think that's an important principle, but not a true double-blind placebo trial.
- Comment that we shouldn't give up on the idea that we can get a placebo. There are ways we can create placebos; don't want to take off this table before we know the agents we're testing.
- Subgroup Chair suggestion that we plan for the worst that we may not get placebos and be glad if we are able to get placebos. It's harder to plan for a placebo and get disappointed.
- **Group consensus on A:B:C:SOC.**
- Regarding randomization and primary analysis:
 - Subgroup Chair mostly cares about whether A beats SOC, B beats SOC, C beats SOC — rather than A beating B
 - We won't have to adjust for multiplicity?
 - Proposal to do a little bit of adjustment for multiplicity. A bad control impacts all comparisons. Want a little more protection. If we include 10 arms and 1 came out with p-value of .04, WG member wouldn't be convinced. Would like a little multiplicity adjustment.
 - If we decided on no multiplicity adjustment, don't think it ruins everything.
 - We will have a little adjustment for multiplicity. The primary focus will be A vs. SOC, B vs. SOC, and C vs. SOC.
- On Randomization:
 - Depends on how many arms. At some point, we need to think about whether we want the SOC to be big if we are making multiple comparisons. If there were 5 arms, I'd probably do 2:1:1:1. With 3 arms, would be much happier with 1:1:1.
 - Some WG members suggest equal randomization.
 - There is not a lot of efficiency to gain by unbalanced randomization.
 - WG member suggests 1:1:1, but if we add 1 more drug, would go with 2:1:1:1.
 - Suggestion that at some point, we should say our desire is 3 arms plus SOC, and let's work towards that. We could make agent prioritization easier if we give the Agent Prioritization Subgroup a target.
 - If we have 4 arms vs. SOC, for a fixed sample size, it's most powerful to use 2:1 randomization.
 - Suggestion that we need to have at least a secondary analysis plan for A vs. B

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- Moving forward:
 - Need to decide what will be adaptive, what we'll have time for, and some idea of our analysis approach, which will be philosophical and broad strokes.
 - We are waiting for further guidance from the FDA to tell us about endpoints, visit schedule, reducing data collection.
 - Hopefully we'll have a spreadsheet of agents by tomorrow to get sense of what the Agent Prioritization Subgroup may decide are our candidate agents. They won't be fully prioritized until the end of next week.

Chatbox

From (b) (6) to Everyone: 02:12 PM

I heard that the people in the meeting this AM were very impressed that this WG was moving "at warp speed."

Would note that the data collection in ACTT is perhaps more intense that we might be interested in.

From (b) (6) to Everyone: 02:19 PM

Agree (b) (6) Excellent summary. thanks

From (b) (6) to Everyone: 02:32 PM

Will we at least be able to get data on rate of progression in the placebo arm of ACT1 with the primary endpoint "clinical efficacy" in ACTT1 to help us plan ACTT 3?

From (b) (6) to Everyone: 02:55 PM

I know the group wanted to move forward as a group for these high-level deliberations. Will we have sub-groups to iron out details for efficiency?

From (b) (6) to Everyone: 02:56 PM

Hi (b) (6) there was some opposition to splitting the group

From (b) (6) to Everyone: 02:56 PM

I remember.

From (b) (6) to Everyone: 02:56 PM

have we ruled out comparisons of A vs B?

From (b) (6) to Everyone: 02:57 PM

Just wasn't sure if there was opposition to splitting at a future point??

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Action Items

Action Items		
	Information	POC
1	Update parameters that were decided at MPSG #4 with the group's new thoughts	Stacey Adam
2	Prepare slides for next discussion	Stacey Adam
3	Begin discussions with the ACTT Investigators	Sarah Read

Key Takeaways

- Decided that platform probably not necessary unless to phase in drugs.
- The protocol should be adaptive to allow for at least one interim analysis for futility.
- Reaffirmed decision to not use multiplicity correction since only testing 3 drugs.
- ACTT3 will use a frequentist analysis approach.
- Primary endpoint selected was time to recovery and collect standardized ordinal scale measurements as secondary endpoint to allow for meta-analysis with ACTT1 and other trials.
- For the secondary endpoints keep it simple, but make sure we get what we need to do good follow-up analyses.
- Still need to discuss trial size yet. This will be based on the kind of effect we're trying to characterize. Need our trial to tease out moderate effects.
- ACTT3 won't deviate from ACTT2 unless there is a good reason.

Recap of Previous Decisions by Stacey Adam

- Lisa's corrected the slides:
 - We may not have ruled out all possible adaptations. Will discuss today. Need adaptive analysis for at least 1 interim analysis.
 - May be 1-2 more drugs come in later and we will be able to bring them in. Do we need this or only using drugs available immediately?
- Group:
 - Should just design this for 2-3 drugs and anything else will go into the *de novo* protocol. The *de novo* shouldn't be so far behind that it would cause problems.
- What about the multiplicity correction?
 - It depends on how many arms there are. Would be better to have at most 3 vs. SOC without making any multiple comparison.
 - AGREED: nixing multiplicity assuming no more than 3 drugs

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- If we do have a placebo, is easier to add later

Discussion of adaptations

- Simplest thing is to borrow from ACTT and have an interim halfway through, have the interim based on events and not people. The decision is dependent on the primary endpoint. And have the caution that we will always look for safety and stop for safety.
- Does it make sense to start with the proposal that will mirror ACTT and see if anyone wants to change any of this.
 - What about the speed? We wanted 2-3 months then heard we need 1 month. Does that affect any adaptations?
 - Can speed up and have an interim analysis that's planned is good, because we may not be able to do it. Hospitals may be past their peak.
 - Change in sample size in ACTT is something that they couldn't do because it accrued too quickly.
 - Getting out early means we just won't be doing anything since the effects will be relatively small.
 - ACTT analysis on Monday, right?
 - Yes, it is interim analysis but it's not really that interim give the study has completely accrued.
 - Lesson Learned: The sample size for interim analysis is going to be much closer to final than expected, so whatever data you've got is there.
 - Don't forget we're accruing to 2-4 treatments and that could slow us too.
 - Hoping we'll match the resources to where we are. I hope we'll learn during this trial and we'll get things done ASAP.
 - Protocols won't slow us down; it will be guided by enrollment kinetics.
- There's a lot of interest on Bayesian analysis but that's more for *de novo*.

Endpoint Discussion

- Thinking about metaanalyses. ISACTT2 changing the endpoint?
 - Thought about it, new model at day 14, changed it to time to recovery, recovery is one of these three states (discharged, or stay just for infection control). Other trials have used time to 2-point improvement on ordinal scale, we opted to time to recovery.
 - What was the basis for the change?
 - The big problem with the ordinal scale is that we decided that we just didn't know enough about what the right day to choose is, if we choose the wrong day, say day 15 and people aren't recovering till 21 days, and we could shoot ourselves in the foot. Such that power is type 1 error rate. We thought about alternatives, like ordinal score averages. Thought about really complicated thing and looking at

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maximum treatment effect over several endpoints but would overstate effect. In the end we said why not just do something everyone will be able to interpret. If someone dies, then someone counts as not having ever recovered at end of 28 days. The deaths are being counted as the worst kind of outcome.

- Appreciate it, but disruptive to field by changing the primary endpoint, as most standardized to the ordinal scale because they assumed this is what ACTT was doing. Its challenging.
- This is our first trial. This is the endpoint for ACTT1. We had it as ordinal but changed it before we actually looked at data.
- That's the point, if we start changing endpoints in the absence of data. This makes it harder to pool results.
- If you have an endpoint that has the potential to have power 2.5% it doesn't make sense. We wouldn't have outside of flu studies using that sometimes. If you know a bit more then it makes a lot more sense to be time to recovery. We were really struggling to figure out what is the best endpoint. I will say this, when we decided to change to time to recovery, everyone who was thinking about this was dramatically relieved.
- There's a lot of trials out there where people have been pushed to take the original approach (ordinal scale). This change is going to be a little upsetting. The most important thing is that people collect the data in that ordinal scale. People don't even know which ordinal scale to use. And we need to make a decision there.
- Ordinal scale was something that psychiatry played around with 20 mins ago.
 - 2 quick questions. Time to recovery gets to the day problem. If you do it at one time point. The power you mentioned, if that was a driver, then the most powerful would be to take the severity scale at 7 points or 8 points. What was the thinking and what was the problem?
 - I was not aware that there were a lot of other groups copying NIH. We don't really have a problem with looking at an ordinal scale, we couldn't have our endpoint without the ordinal scale. If other people are using the ordinal scale, then you can have reproducibility. When considering the average across days and subtracting the baseline, which I thought was going to be much more powerful, and we heard from some clinicians that that wasn't easy to interpret. That's what they said. It didn't turn out to be as powerful as we thought because its highly dependent on assumptions you make on how highly correlated scores are on neighboring days. We'll have this blind endpoint and would be able

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- to help us. Thought about it a lot and talked with people at the FDA and thought it was too complicated to be able to convince everyone.
 - I was going to ask the agency about the endpoint of time to recovery.
 - Seemed to be relieved to see that vs. what we had considered.
- FDA guidance soon?
 - Yes, anticipating by next week, it will be helpful but not the holy grail. Will present options that will present clinical benefits. Some will come from ACTT1 and some from Chinese remdesivir trial. Will need to be a data driven discussion, which will be soon but not next week.
 - We can measure everything and compute anything, but we need a decision maker etc. and we only need it just before the first unblinding. The problem is the power and we need that for analysis. If we make sure we collect information on the 8-pt. scale, then we'll be able to compare across. It's crucial to, whatever we decide is the primary endpoint, then whatever is happening we can use elsewhere.
 - Would it be possible to base the decision on the final sample variable and the results from ACTT1? Endpoint is not supposed to be a suicide pact and keep you on a useless path. Can we preplan to be able to reevaluate when data come out from ACTT1 to be able to readjust sample size analysis strategy etc.?
 - We can take a conservative approach so that we can get to a closer version.
 - We have no clue on effect size. We need to understand but it's not as if we're going to be able to make a definitive answer to these questions till these data come in.
 - It's important to do time to recovery here, if you use log-rank on that then it'll be dependent on only that parameter. If proportional odds model, then you need to know about the states and it's a lot more speculative than a time to event.
 - Not too hard to power with continuous severity score either.
 - One thing we need to understand also, is its more than a statistical issue, need to understand the endpoints and ordinal scale endpoints. Need to balance this from a statistical and medical perspective because need to see blending of endpoints and it's probably orthogonal and update the analysis to update the endpoint.
 - The ordinal and the time are correlated. Need to understand the correlation to time to recovery and ordinal. Update primary endpoint and use the final analysis from the remdesivir trial.
 - Base that on external data not internal
 - Still need to understand these correlations then otherwise we need to understand correlation on these 2 endpoints.
 - Sounds as if we're going to be severely underpowered in any case.

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- Based on the fact that we don't know what is good, we could end up with wrong day low power right day high power. It's undesirable to base an endpoint on guessing the course of the disease
- **Could put in time to recovery and have an asterisk on pending results of ACTT1, don't know how quickly someone will be able to take the results you're looking at. Comparison of endpoints isn't high on the list for many people, but it is for us**
- **Decision. Time to recovery, with an asterisk, and collect ordinal points for later and for meta analyses.**
 - Only thing to bring up, in the absence of a placebo then the next question is bias in endpoint ascertainment. The ordinal scale is pretty good outside of requiring ongoing medical care and so may need to be a bit more prescriptive on ACTT3.
 - That's defined based on components of ordinal scale. Some components of the ordinal scale may be less useful than you might think. If ventilators are on short supply people may not get them even though they need them. So, we felt more confident in that than in all the others. That led us to believe that that was a good endpoint, time to recovery.
 - At Merck looked really closely at ordinal scale and a real interest on something that might be more straightforward and easier to understand. The differences between the points aren't the same.
 - One nuance to the time to recovery and hospitalization where people could be better but waiting for a place to go

Other Outcomes

- Think we want simple in this trial too and want to support any potential primary endpoints we might land on. Can't cut too much out. Some people commented ACTT1 was more like a research protocol.
- May need to talk to Clinical Trials Capacity, they might have some other simple solutions. May be able to help us get data we want and not be overly burdensome.
- Guiding principles need to be more data so we don't find out after like they did in ACTT1, that we need something we didn't have.
- Need to focus on objectivity and maybe open label.
- The fact that we can collect data better doesn't mean we should. Then we just collect more, and it just sits in more junk piles and we just send to the FDA.
- Automated data collection would be good, but we need to go through and figure out what we need.
- ACTT3 should not be guinea pig for new tech.
 - E-consent and some telehealth follow-up for post hospitalization follow-up. They weren't going crazy.

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- What would really make the trial easier would be automated extraction from EHR...don't know about network within ACTT1. Survey to networks and sites goes out today.
- Direct EHR monitoring, its being used in COVID more but a lot of sites are holding firm against it.
- Can't put barriers across sites.

Procedures for safety?

- How do we balance procedures needed for each drug? Do we tailor or have it somewhere in between?
- In most you balance and try to find the LCD and add what's drug specific to that arm. Guides lowering of dose etc. have sham if placebo and double blind but if not its fine. Have std safety and be drug specific for drug/placebo.
- In bet trials that's tougher, and part of our goal here is to figure out what matters most to patients.

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Chatbox

00:29:44 menons09: Agree with Mike. As long as ordinal scale is collected we should be fine. Primary endpoint should be powered based on time to recovery which is more meaningful and gives the trial to succeed

00:30:23 menons09: We should be able to pool and do the meta-analysis to compare.

00:30:38 Stacey Adam: Thanks Sandeep. I would agree

00:30:41 markde: Don't get me wrong - I agree that the ordinal endpoint is not intuitive. But we and others have adopted this approach for consistency.

00:30:45 Stacey Adam: we can have it as a secondary

00:31:19 menons09: Consistency is fine Mark as long as it is not a primary endpoint. It can be a key secondary endpoint

00:31:30 markde: I think its fine.

00:31:54 menons09: even the ordinal scale endpoint does not have enough data.

00:32:21 markde: FDA has argued strongly for the ordinal scale in hospitalized Flu

00:33:22 menons09: There is also heterogeneity of the patient population and ordinal scale is hypersensitive to multiple confounders like patient severity, time, etc.

00:33:38 markde: I need to sign off. Back at 11

00:34:09 Stacey Adam: Thanks Mark

00:38:14 menons09: we need to do some thinking on the correlation between time to recovery and ordinal scale endpoint.

00:38:43 menons09: Then we can use it in the IA in the blinded way to update the endpoint

00:38:50 Stacey Adam: Agreed, but do we need to do that ahead of drafting or can it be done in parallel?

00:39:02 Stacey Adam: True

00:39:03 menons09: It is not just a statistical issue, need to balance it a little

00:39:59 Keith Gottesdiener: agree, this is not primarily a stat issue - it just is masked in the stat discussion

00:44:55 sam bozzette: agree with Lisa

00:45:12 menons09: Agreed Lisa

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00:55:32 **Peter Wung:** How do we balance the procedures needed to monitor for safety across the 2-5 compounds which will likely have different safety profiles?

00:55:33 **Wachtel, Jonathan:** I'll take this back to Karen

00:56:30 **Wachtel, Jonathan:** on Clinical Trials Capacity WG

00:56:44 **Stacey Adam:** Thanks Jonathan

01:00:46 **menons09:** Remedisivr just read out - primary endpoint with time to clinical improvement

01:01:02 **menons09:** Trial failed

01:01:09 **Eric Hughes:** oh no

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Action Items

Action Items		
	Information	POC
1	Update times on the timeline for “select optimal structure and statistical design” and “Select top 2-5 candidates”	Stacey Adam
2	Consider necessary and desirable design elements for the <i>repurposed</i> ACTIV Master Protocol and be prepared to finalize by April 24	Master Protocol Subgroup
3	Consider necessary and desirable design elements for the <i>de novo</i> ACTIV Master Protocol	Master Protocol Subgroup
4	Distribute document from Mike Proschan	Stacey Adam
5	Schedule new meetings each day for the next two weeks including one of the two weekend days	Stacey Adam/ Elizabeth Kim

Key Takeaways

- Master Protocol Subgroup reached consensus and confirmed plan to move forward in drafting ACTT3 Amendment as a necessary first step, and in parallel create a *de novo* ACTIV Master Protocol.
- In terms of messaging, WG emphasizes to ACTIV leadership that the *de novo* ACTIV Master Protocol is the vehicle truly needed.
- Subgroup decided to design a trial that will allow for fast screening for compounds with high response rate interim assessment (and perhaps binding futility) to triage compounds, but with option to allow the trial to proceed to full registrational trial if drug looks promising

Reviewing Updates to the Master Protocol(s) Action Items List and Timeline

- Brief overview of updates to action items list and timeline based on Subgroup meeting yesterday, 4/20: Added informed consent, creation of assignment algorithm, reduced time on left hand side, added more time to *de novo* to ensure enough time
- Feedback on *De Novo* steps and timelines
 - Comment that “Select optimal structure and statistical design” is the most difficult and will be rate limiting. Unless it’s streamlined and with a unique procedure, it will take longer than 1-2 days to resolve. WG will need to resolve this before moving forward.
 - Suggestion to take time out of “identify top 2-5 repurposed drugs” because some of the work will be done by the Agent Prioritization Subgroup.
- The action items list and timelines can be a living document. WG members should feel free to provide further feedback, but for now, this is the timeline we will be moving forward on – first

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starting with “repurposing” the ACTT trial and drafting an ACTT3 Amendment, and then writing the *de novo* ACTIV Master Protocol in parallel.

- The assumption is that for the ACTT3 Amendment, NIH will be the sponsor for this study (NIH is already the sponsor for ACTT). For the *de novo* ACTIV Master Protocol, it is not certain that NIH will be the sponsor.
 - If NIH is the sponsor, it would make IND easier.
 - Even if NIH is sponsor, there can be flexibility in the contracting with assistance from FNIH if needed in the structure.

Discussion on whether to pursue ACTT3 Amendment Drafting

- Discussion on whether to pursue “repurposing” ACTT trial and on “phases”:
 - Suggestion that the WG needs to decide what is considered “enough” – if the group pursues structure from ACTT1 and 2, it will take a considerably long time to get through the list of compounds. If we make all the compounds suitable for registration, we will probably get through the list of compounds in 2030.
 - The UCSF I-SPY COVID trial is taking creative approaches and discussing with the FDA the boundary between “just enough” to getting a drug registered and figuring out what works.
 - From perspective of drug developers and pharma, there are no Phase 3 agents due to the paucity of data.
 - We’re looking to screen agents and determine if there is any activity sufficient to progress.
 - Suggestion to stop thinking in phases. Many of the molecules we are considering have already been approved. Question we should consider: what do we need to find so that we feel comfortable and the regulators are comfortable that we can use the molecule broadly? Exactly what is the bar? There are scientific, clinical, and regulatory components in thinking about what is the bar.
- Discussion on whether the group still wants to try to repurpose ACTT. Can we actually modify it to be a screening protocol because that is not what it is now.
 - Yes, ACTT3 may be different from ACTT2 which had a factorial design, a good number of patients per arm, and was powered to get clear answers for modest effects with the drugs. ACTT3 could stipulate that the drug doesn’t have a 40% effect, for example, it’s not good enough for us to spend a lot of time and effort on it.
 - WG member would like to see an ACTT3 take 6-7 compounds in well-designed phase 2-3 studies with 500 people all conducted in separate control trials. Need a study that will answer the question in a few weeks – can ACTT3 be made to do this or not?
 - Suggestion that another way to repurpose is to take studies in the field and pull them together somehow, from all pharma-sponsored well-designed trials existing
 - Agreement that there are poorly designed trials that are problematic. There are also well-designed trials that aren’t going to accrue. There needs to be some effort

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to canvas what's out there. It's difficult to discern what's being adequately studied, and what that means.

- Group consensus to avoid using "Phase 2-3." We are attempting to see if there is a signal for efficacy, and presumably we're dosing at a dose that is at least supported by prior data. The idea is to see if any of these drugs are things that we could be using right now to help treat patients.
- Co-Chair summary of how the two proposals for how to repurpose ACTT:
 - (1) Take 5-6 trials with 500 patients or more. If there's some efficacy seen, take it up as a treatment.
 - (2) Having smaller studies where we are looking for a big effect to go onto an ACTT3 trial
 - Right now, ACTT is designed such that if there is efficacy seen, that will become Standard of Care.
 - NIAID is drafting a protocol called BET – Big Effects Trial – which is designed to enroll several small arms, each looking at different interventions to see which will give big signal to then feed into ACTT. Now, they're designing BET To feed into ACTT.
 - Co-Chair thought WG would repurpose ACTT to put 2-4 candidates in, and if shown as having efficacy, it would become part of Standard of Care vs. with the *de novo*, the focus is on which of these 6-8 candidates is worthy of moving on slightly bigger trial that would give us more confidence in clinical efficacy.
- Suggestion that we need to decide what is enough to say that this is a really good answer? We need to think about what the definition of getting an answer is – it might be 200 patients, powered for larger effect size.
- WG member does not think it is a good to have small trial with some suggestive, not definitive, evidence. Strongly believe if Kaletra, for example, had gone to 400 in clinical population instead of 200, they would've had statistically significant results. The data was promising for the trial, but the conclusion was that there was no effect. This should be a design consideration.
- A lot of what will drive how we use the protocols is what is available. Candidates that go into a redefined ACTT will be those that are immediately available on large scale, then those to screen in large numbers in new Master Protocol. We need to look at things in terms of speed and availability.
 - There are at least 6 companies working on monoclonal and at least another 10 bio techs. In the next 6 months, 6-12 monoclonals will enter into trials. At some point, need to get them in trials and start placing bets. Let's try to figure out a minimum way to give clear answer.
- Through the appropriate use of adaptation, the Master Protocol(s) can be written in a way whereby agents can come in rapid succession and rapidly removing those that have no potential of being meaningful after first 100 patients.
 - It would be useful to have a binding futility rule.
 - Such a protocol would allow us to screen a relatively large number of candidates, each of which has low prior likelihood of success and simultaneously develop a robust dataset of

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those with likelihood of success. We can use statistical machinery and regular interim looks with clear criteria to do both things simultaneously.

- Stacey Adam reminder to the group that the WG's short-term mandate is to develop something quickly. The "repurposing" timeline currently puts us activating at end of May 2020, and Dr. Francis Collins wants us to activate mid-May.
 - We need to decide now: are we still repurposing? If so, are we repurposing ACTT, and what does that need to look like?
 - BET is not drafted yet.
 - Concern that repurposing won't help solve our problem. We can help test 1-2 drugs, but that won't help in long run. We can't launch machinery that will appropriately test a range of candidates in a matter of a few weeks. It would be cosmetic. We need to provide clear expert guidance to NIH leadership on what will solve this problem.
 - If the idea is to get 2-3 things tested immediately, then we need to repurpose ACTT. We can communicate that the *de novo* ACTIV Master Protocol is what we'll need to spend more time on. The message of the WG is really that this *de novo* Master Protocol is the vehicle we really need.
 - We need to give Francis a quick win. Worthwhile to get a couple of molecules in.
 - The goal is to provide useful information to care of patients. The hybrid approach is fastest way to get there in short and long-term.
 - Suggestion to split the Master Protocol Subgroup into smaller teams – one to draft ACTT3 and the other to focus on *de novo* Master Protocol. Not agreed upon by group; they feel the group should work all together. There are potential synergies between drafting an ACTT3 and creating *de novo*. As you work on one, you can bring the best into the *de novo* ACTIV Master Protocol.
 - Group in consensus that repurposing ACTT is a necessary first step to meet the timelines we've been asked. ACTT3 needs to be nimbler and encompass multiple drugs.

Review of Master Protocol Basic Structure, Sub-Chair Lisa LaVange

- We can get going with the basic structure.
- A Master Protocol involve part infrastructure, part study design, is meant to test multiple drugs, possibly multiple therapies or both.
- There are structural things that make it work well – like separating the common from specific, working with documents in amendment form to add drugs, and to think about common screening/recruitment – anything to do in a common/centralized form
 - May be a platform or adaptive trial
 - "Platform" means things come and go.
 - Trial can go in perpetuity and can stop.

Tuesday, April 21st, 2020

- Everything does not have to be ready at the same time.
- Can put drugs in and take out according to specific rules
- If lucky, can share control patients but not always
- If done correctly, may be able to replace Standards of Care with minimal interruption
- Adaptations are up to what you want to do, or you can do without any adaptation. Usually, there is some adaptation. 4 common adaptations are listed on the slide – none of which we have to use.
- Assumptions & Questions
 - If we do a repurposing protocol, should assume we have bucket of drugs ready to go in the near future, top tier drugs, with enough information to put them in top tier
 - We will use the ACTT Network and try to write ACTT3 with a protocol amendment, which means something special for ACTT. It would be adding another section to the body of the protocol.
 - We may change endpoints and visit schedule. We may not measure everything every day. Standards of Care may change over time.
- Simplest questions on how we do the comparison study
 - Will we start with group of drugs, or few ready and add more?
 - Who has placebo? Based on that, how to do masking? If look at ACTG and other protocols, seems uniform that placebo is important.
 - Are we really looking at drug vs. placebo / drug on top of Standard of Care / placebo on top of Standard of Care?
 - Can we share control patients or not?
- Few more issues
 - Master protocol and multiplicity – we argue strongly not to look at multiplicity.
 - Distribute Mike Proschan's document.
 - Randomization questions – tie into placebo, Standard of Care, ability to bind
 - Responsive adaptive not popular – we need to vote on yes/no
 - Will we do any adaptations?
 - Frequentist or Bayesian?
- Other things we may need to start
 - Some type of graduation criteria
 - Concept of Phase 2-3 design. We need to somehow have earlier screening based on some criteria of chance of success and weed out not exciting drugs as quickly as possible.
 - *De novo* populations: we haven't talked about getting out of hospital for recruitment, and this may have an impact. Endpoint will change.

ACTIV, Therapeutics-Clinical Master Prioritization Sub Group Working Group Meeting 4, Key Takeaways

Tuesday, April 21st, 2020

- (b) (6) felt very strongly that we should be (b) (5)
 - R&D consortium agreed with Jane's recommendation, but this doesn't mean they can't be under one umbrella. Administratively, the two populations can be under one umbrella but have two completely design parts.
- Someone needs to pool this data together.
 - Suggestion – if we agree that ACTT3 is our WG's first goal, we should just focus on the first 2 slides – assumptions & questions.
 - Decision to have more frequent meetings moving forward for Master Protocol Subgroup, another meeting over the weekend

Chatbox

From (b) (6) to Everyone: 01:53 PM

Speaking of prioritization of drugs, will there be the possibility of (b) (5) we will need to address that type of design as well (b) (5)

From (b) (6) to Everyone: 01:54 PM

We hope so (b) (6)

From (b) (6) to Everyone: 01:59 PM

I am a bit confused - are we (b) (5) soon?

From (b) (6) to Everyone: 01:59 PM

Not yet. After we get through (b) (5)

Action Items

- Dr. Payton will finalize the network inventory spreadsheet based on the additional networks suggested by the Sub-WG during this meeting and any networks specifically mentioned in the ACTIV press release.
- Sub-WG members will contact specific networks to solicit their interest in participating in ACTIV in order to build an advance pool of high-capacity trial sites:
 - Dr. Payton: NIAID (ACTG, HPTN, HTVN)
 - Dr. Kurilla: NHBLI PETAL with outreach to Dr. Goff to identify additional NHBLI networks
 - Dr. Stein: TIMI and DCRI

High-Level Meeting Summary

The Clinical Trial Capacity Inventory Sub-Working Group (Sub-WG) reviewed progress toward a comprehensive identification of networks that may participate in ACTIV trials. The Sub-WG discussed and finalized a spreadsheet-based inventory of 36 networks that may meet the criteria for a Tier 1 or 2 designation (i.e., that may be capable of running ACTIV trials within 6 weeks or within 6 to 12 weeks, respectively). Inventory Sub-WG members agreed to contact six of the likeliest networks in order to solicit preliminary interest in participation. Simultaneously, the current full inventory will be shared with the Survey Sub-WG for collection of more detailed information regarding network capabilities and capacity.

Below is a summary of the key discussion themes.

Content of the Inventory

Current Inventory

The Sub-WG has defined a network as one with a Leadership and Operations Center to provide scientific and administrative leadership, central operations, and communications; Statistical and Data Management Center to provide biostatistical leadership and centralized data management; Laboratory Center to provide laboratory services necessary to conduct clinical research; and portfolio of Clinical Research Sites where participants are screened and enrolled.

Participants reviewed a draft inventory assembled by Dr. Payton of three kinds of trial networks organized by category of institutional affiliation: (1) NIH Institutes and Centers, (2) academic research institutes, and (3) other kinds of institutions. The Sub-WG further developed the initial list to include 36 total networks, which they agreed was an appropriate number to share with the Survey Sub-WG.

Participants believed that all identified networks, regardless of their likelihood of participation, should be contacted for assessment of capacity and capability. They also discussed specific NIH and academic networks that hold particular promise for ACTIV, including NIAID's infectious disease networks, NHBLI's lung trial networks, and NCI's Women's Health Initiative, whose tens

of thousands of enrollees may be among the older populations most vulnerable to COVID-19.

(b) (6) noted that (b) (5) , but participants agreed (b) (5) of relevance to ACTIV, (b) (5) .

Future Inventory Development

Participants agreed that surveys may act as an indirect network identification tool: as they are circulated, their visibility may attract additional interested networks. The Inventory Sub-WG may also, after the first survey round, proactively expand its identification of networks affiliated with other institutions (such as CROs and the VA). During this subsequent inventory, the Sub-WG may look specifically for networks that conduct research in areas of interest to the Therapeutics-Clinical WG, such as cardiovascular research. It may also consider evolving comorbidities that make new networks ideally suited to evaluate specific populations.

Outreach Plan

Participants agreed that the Inventory Sub-WG and Survey Sub-WG both have a role to play in network outreach.

Immediate Inventory Sub-WG Outreach

Participants identified high-priority networks that its members will contact this week in order to achieve several “quick wins” that build a pool of strong respondents when the survey is ready. Prioritized networks include:

1. **NHBLI networks**, including the PETAL network, which is currently running a hydroxychloroquine trial and has expertise in respiratory distress
2. **NIAID networks**, including ACTG and HPTN, which have strong data management and operational infrastructure and large numbers of sites
3. **TIMI and DCRI**, which have conducted large outcome trials

Survey Sub-WG Outreach

Participants discussed how the Survey Sub-WG can maximize replies from networks. They agreed that the first round of network outreach can leverage NIH points of contact. NIH leaders are best positioned to convey to network PIs the significance and urgency of this effort, but they can also alleviate the burden of participation by providing already available information about networks to the Survey Sub-WG.

Importance of Integrated Efforts

Participants emphasized that continued integration across WGs is critical to survey success. For example, the Survey Sub-WG is planning a two-part survey that collects information about both network capabilities and site capabilities; the latter should be influenced by the work of the Master Protocol Sub-WG, whose parameters will determine the kind of site capacity that is needed. Integrated messaging is another priority as the survey becomes a public document and industry peers begin to discuss it with each other.

Appendix A: Participants List

WORKING GROUP MEMBERS

Larry Corey, MD, *President and Director Emeritus, Fred Hutch*

Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

Peter Stein, MD, *Director of CDER's Office of New Drugs, Food and Drug Administration*

Janet Woodcock, MD, *Director of the Center for Drug Evaluation and Research, Food and Drug Administration*

CLINICAL TRIAL CAPACITY WORKING GROUP CO-CHAIRS

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences*

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer, Research Partnerships, Foundation for the NIH (FNIH)*

Michael Santos, PhD, *Associate Vice President, Science, Foundation of NIH (FNIH)*

Karen H. Tountas, PhD, *Scientific Program Manager, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Jonathan Wachtel, MBA, *Manager, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Action Items

- Dr. Payton will develop a spreadsheet on Basecamp that will list all suggested clinical trial networks and information associated with each network criterion (e.g., size, statistical core, etc.).
- Sub-WG members will provide network suggestions, with a focus on Tier 1 recommendations, to Dr. Payton, who will update the spreadsheet and share the finalized document with the Clinical Trial Capacity Survey Sub-WG on Tuesday.
- Dr. Kurilla will share with Dr. Payton information collected by NIH about current NIH IC clinical trial networks.
- Dr. Stein will share with Dr. Payton information about other potential clinical trial networks, such as the TIMI Study Group, Duke Clinical Research Institute, and ex-US networks.
- Dr. Tountas will circulate a list of Sub-WG members' mobile phone numbers to facilitate quick contact between members.

High-Level Meeting Summary

The Clinical Trial Capacity Inventory Sub-Working Group (Sub-WG), led by Dr. Larry Corey, convened to compile a comprehensive list of clinical trial networks to be shared with the Clinical Trial Network Survey Sub-WG.

Sub-WG members adopted a tiered structure to identify and assess clinical networks. They decided to prioritize the identification of "Tier 1" networks with experience in clinical trials and resources to launch a trial within the COVID-19 environment within 6 weeks. They will discuss networks that require additional resources and infrastructure (labeled Tiers 2 and 3) in a future meeting.

Sub-WG members will create a spreadsheet compiling all networks suggested by WG members and classifying each network by Tier of readiness for COVID-19 efforts and prioritized capabilities. The Sub-WG will share the completed spreadsheet with the Clinical Trial Network Sub-WG, which will create and share a survey with Tier 1 networks this week.

Below is a summary of the key discussion themes.

Prioritization

The goal of this Sub-WG is to provide the Clinical Trial Capacity Survey Sub-WG with a list of networks that can eventually be matched with COVID-19 clinical trials based on their specific capabilities (e.g., access to specific patient populations or experience in pragmatic clinical trials).

Participants discussed whether to include specific clinical trial sites in addition to established multi-site networks. To maximize efficiency and speed, they decided to prioritize networks at this time and to revisit the involvement of individual sites later. Participants also discussed

whether to include networks of observational studies or pediatric populations, but decided that these networks are not high priority at this time.

Participants stressed the need to include clinical network sites with the capability to assess patient populations at every stage of disease progression—from pre-disease prevention, to inpatient and ICU treatment, through outpatient treatment. While each network would optimally work across these stages, networks with capabilities at an individual stage will be leveraged appropriately through the site and trial matching process. For example, networks with access to asymptomatic patient populations, but without ICU capabilities, will be matched with a clinical trial focused on prevention, whereas networks with inpatient and ICU capabilities will be linked to vaccine trials.

Categorization

Participants developed a tiered system (Tiers 1, 2, and 3) to classify the readiness of clinical trial networks to be leveraged for COVID-19 efforts. Tier 1 indicates networks ready to be leveraged and fully functional within 6 weeks, whereas Tier 2 and 3, respectively, require 6 to 12 weeks, or more than 12 weeks, to acquire additional infrastructure or resources to be fully activated. Each network will be further classified based on the following information:

- Network size (i.e., number of sites)
- Leadership and operational center
- Statistical Core
- Laboratory Core (not necessary for drug repurposing clinical trials)
- Central IRB
- Previous experience in conducting clinical trials with identified sites and PIs

For Tier 1, participants identified PCORnet, I-SPY, and NIH institutes and centers (ICs; e.g., NIAID, NCI, NIMH, NICHD, NHLBI, NIGMS) because each could be leveraged quickly and meet most of the criteria listed above. They also identified networks that may require additional time and resources (e.g., sites associated with Kaiser Permanente clinical sites, industry, insurers, CROs, military research programs, VA).

NIH is currently deploying initiatives to gather clinical trial network capability of each NIH IC, separately from COVID-19 efforts. Dr. Kurilla will share current findings from this initiative with Dr. Payton, who has begun contacting NIH ICs to discuss current clinical trial networks. Dr. Stein will also share with Dr. Payton information about other potential clinical trial networks, such as the TIMI Study Group, Duke Clinical Research Institute, and ex-US networks (particularly in Canada).

Appendix A: Participants List

WORKING GROUP MEMBERS

Myron Cohen, MD, Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill

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Michael Kurilla (Co-Chair), MD, PhD, Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences

FNIH STAFF

Michael Santos, PhD, Associate Vice President, Science, Foundation of NIH (FNIH)

Karen H. Tountas, PhD, Scientific Program Manager, FNIH

Jonathan Wachtel, MBA, Manager, Deloitte

Bethany Stokes, MS, Writer, Rose Li and Associates, Inc.

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Drs. Elizabeth Desrosiers and Michael Kurilla, convened to review the sub-working groups' (sub-WGs') membership, remits, and meeting cadence and the master protocol (MP) options strawman developed by the Clinical Therapeutics WG. Members also watched demonstrations of a site-tracking system and of Basecamp (which will be the project management platform for ACTIV).

The WG agreed that the next step will be to schedule the first meetings of the sub-WGs within the next 3 days.

Below is a summary of the key discussion themes.

Clinical Trial Capacity WG Sub-WGs

This WG will now have three sub-WGs:

- Survey Development will develop surveys and identify targets: Goff (lead), Bascles, Desrosiers, Dickens, and Nayak
- Clinical Trials Network Inventory will develop an inventory of networks and known capabilities: Corey (lead), Cohen, Payton, Stein, Resnansky, Woodcock
- Innovation will identify innovations that will enable execution of clinical trials: Srinivasan (lead), Doroshov, Kurilla, Vincent, Woodcock

The leads will schedule their sub-WGs' first meetings for today (April 17) or over the weekend to initiate and make progress on the goals, which will be reported to the overall WG on April 21 and the ACTIV leadership team on April 22. The leads will work with Dr. Tountas and Mr. Wachtel to schedule the meetings (which may be supported by a science writer).

Master Protocol Options Strawman

The WG will use the patient populations defined by the MP Subgroup of the Clinical Therapeutics WG, with input from the CTC WG, to inform its inventory of networks and known capabilities and to shape its development of surveys and targets. The MP Subgroup has defined four patient populations to address with existing MPs or a new MP(s):

- Individuals who require care for hypoxemia (hospitalized/moderately ill, non-ICU)
- Individuals who require treatment to prevent mortal/morbid complications (critically ill/ventilated, ICU)
- Infected individuals observed at home, with the aim of preventing progression (outpatient/ ambulatory ill)
- Healthy noninfected individuals, with the aim of intervention/prevention of disease (prophylaxis/prevention)

To meet its mandate to develop an MP and identify therapeutic candidates within 10-14 days of project start and to begin clinical trials that can report patient outcomes by June or July, the MP Subgroup prioritized these patients populations to be addressed in the following order: (1) hospitalized/moderately ill and critically ill/ventilated; (2) outpatient/ambulatory ill; and (3) prophylaxis/prevention.

However, this WG may need to consider the moderately ill and critically ill patient populations as separate, because the information needed to assess a network's capacity to study those populations may differ.

The WG members posed the following questions, largely related to nuances within the participant population definitions:

- How is prevention defined? Prevention of infection? Prevention of disease progression?
- How will prevention, which takes the form of both vaccines and nonvaccines (e.g., antivirals and standard of care), be partitioned?
- Many non-infected individuals are not healthy (e.g., individuals who live in nursing homes or assisted living facilities or have conditions such as pulmonary disease that place them at high risk). Do they still fall within Priority 3?
- Should individuals in the prophylaxis category be referred to as participants rather than patients (with reference to the strawman diagram)?
- Should there be a fifth category for convalescence?

The need to work in close consultation with the MP Subgroup of the Clinical Therapeutics WG remains high. Goff and an industry representative (to be determined) will represent the CTC WG on the MP subgroup.

Innovation

The COVID-19 environment poses challenges to executing clinical trials. The WG agreed that networks should have a demonstrated capacity for innovation (use of adaptive methods, registries, telemedicine) and time-sensitive intervention. One example is the SIREN Network, which is funded by the National Institute for Neurological Disorders and Stroke (NINDS), the National Heart Lung and Blood Institute (NHLBI), and the National Center for Advancing Translational Science (NCATS).

The WG agreed that the Innovation Sub-WG will further explore Merck's COVID-19 Geo-Mapping Site tool (built on Qlik software with data from Johns Hopkins University and Spectrum). This system may inform decision makers' understanding of how clinical trial sites and COVID-19 outbreaks will intersect and may be used to improve clinical trial planning and response.

Next Steps

The sub-WG leads will work with Dr. Tountas and Mr. Wachtel to schedule the first sub-WG meetings; sub-WGs will begin executing their activities to reach WG goals.

Appendix A: Participants List

WORKING GROUP MEMBERS

Lionel Bascles, PhD, Senior VP, Global Head of Clinical Sciences & Operations, Sanofi
Myron Cohen, MD, Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill
Larry Corey, MD, President and Director Emeritus, Fred Hutch
Elizabeth Desrosiers (Co-Chair), MS, PMP, Executive Director, Clinical Sciences and Study Management, Merck
James Dickens, Program Manager, National Center for Advancing Translational Sciences
David Goff, MD, PhD, Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute
Michael Kurilla (Co-Chair), MD, PhD, Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)
Seema Nayak, MD, Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases
Manizhe Payton, Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases
Laura Resnansky, Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech
Badhri Srinivasan, Head, Global Development Operations, Novartis
Peter Stein, MD, Director of CDER's Office of New Drugs, Food and Drug Administration
Michael Vincent, MD, PhD, Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer
Janet Woodcock, MD, Director of the Center for Drug Evaluation and Research, Food and Drug Administration

INVITED PARTICIPANTS

Jintanat Ananworanich, MD, PhD, Bill & Melinda Gates Medical Research Institute
Christine Colvis, PhD, Director, Drug Development Partnership Programs, NCATS
Penny Heaton, MD, Chief Executive Officer, Bill & Melinda Gates Medical Research Institute
Eric Hughes, MD, PhD, Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis
Ashley Parker, PhD, Special Assistant to Acting Chief of Staff to the NIH Director, National Institutes of Health
Laura Resnansky, Vice President, Global Head of Clinical Operations - Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Roche/Genentech

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer, Research Partnerships, Foundation for the NIH (FNIH)*

Stephanie James, PhD, *Senior VP of Science, FNIH*

Joseph Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate VP of Science, FNIH*

Karen H. Tountas, PhD, *Scientific Program Manager, Science, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Rosa Marie Alvarez, *Consultant, Deloitte*

Margaret Anderson, *Managing Director, Deloitte*

Nina Gonzalez, *Senior Manager, Deloitte*

Elizabeth Kim, *Senior Consultant, Deloitte*

Benjamin Stratton, *Senior Consultant, Deloitte*

Brett Tolman, *Manager, Deloitte*

Nancy Tuveesson, MBA, *Writer, Rose Li and Associates, Inc.*

Jonathan Wachtel, *Manager, Deloitte*

Appendix B: Chat Transcript

From (b) (6) to Everybody 00:20:08

We also need to have an idea and likelihood that the existing networks can expand; how easy is it for them to add additional sites administratively

From (b) (6) to Everybody 00:23:12

I'd be happy to join the master protocol group as a liaison from this group. I noticed that NHLBI is not represented, so i could also introduce that connection.

From (b) (6) to Everybody 00:24:48

Currently (b) (5) is envisioned to fall within the therapeutics groups, but the importance of connection between the Vaccines and Therapeutics Working Groups on prevention (models, protocols, etc.) is definitely recognized.

From (b) (6) to Everybody 00:27:20

Hi. My experience is the thinking about (b) (5) "sit" better with the Vaccine group than the therapeutics group or at least considerable collaboration. Certainly the infrastructure, investigators and populations to be studied are very different.

From (b) (6) to Everybody 00:29:05

In the slide (b) (5) participants who are NOT considered patients

From (b) (6) to Everybody 00:38:51

Would like to weigh in for TX-Clinical group

From (b) (6) to Everybody 00:55:44

(b) (5)

From (b) (6) to Everybody 00:57:56

Can we use (b) (5)

From (b) (6) to Everybody 00:58:14

Yes.

From (b) (6) to Everybody 01:00:50

(b) (6) if anyone needs my email

From (b) (6) to Everybody 01:06:16

Apologies, I experienced a total internet failure

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (WG), co-chaired by Drs. Elizabeth Desrosiers and Michael Kurilla, convened to discuss and strategize on approaches to fulfill its charge to maximize the capacity and utilization of clinical trials to identify effective therapeutics and vaccines for COVID-19. To start, the WG will develop an inventory of the clinical trial networks (CTNs) and sites that have the capacity to conduct trials of the therapeutics prioritized by the Clinical Therapeutics WG and to report outcomes by June or July.

WG members highlighted the importance of moving sites that are fit for purpose and can quickly launch a new trial into clinical trials as soon as possible, especially trials of repurposed compounds. They agreed that the traditional approach to identifying sites for feasibility studies is not agile enough to address the evolving nature of COVID-19.

The WG decided to form four subgroups to facilitate rapid execution of activities.

- Clinical Trial Network Inventory sub-WG (Inventory of networks and known capabilities)
- Survey Development sub-WG (Development of survey(s) and identification of target(s))
- Patient Population sub-WG (define patient populations)
- Innovations sub-WG (Identify innovations that will enable execution of CTs)

Overall, this WG will work in close consultation with the Therapeutics - Clinical WG.

Below is a summary of the key discussion themes.

Inventory of Clinical Trial Networks

In a parallel effort, National Institutes of Health (NIH) staff are developing an inventory of all NIH-funded CTNs, which will capture information about their capacity, locations, and patient populations. NIH is very interested in using the WG's input to shape the parameters of this inventory. For example, the WG may identify other non-NIH-funded networks such as PCORnet and clinical trial sites run by pharmaceutical companies or their contracted research organizations and academic centers.

The WG suggested that any inventory efforts should consider including groups that work outside the infectious disease space (e.g., cancer, cardiology) but have expressed interest in contributing to this effort or have a demonstrated capacity to study therapeutic interventions.

The WG discussed the relative importance of true clinical trial networks over single sites linked together in a multicenter trial, with a coordinating center and ancillary services, for just one specific trial. The WG agreed that the ability of such sites to pivot beyond a specific trial to new type of interventions would have to be evaluated on a case-by-case basis.

Define Patient Populations

To develop a useful inventory of CTNs and their characteristics, the WG must first determine the types of studies the CTNs will conduct (e.g., "decide the what before the how") in close coordination with the Therapeutics WG. Therefore, the WG decided that a next step will be to

define patient categories and their endpoints, which will inform development of a survey to collect information about network/site capacity. If patient categories are based on an ordinal scale for clinical improvement, then outcomes can be more easily envisioned and compared across studies. WG members suggested the following patient categories that could be amendable to master protocols: outpatient COVID-negative, outpatient COVID-positive, hospitalized, hospitalized and receiving CPAC, hospitalized and receiving mechanical ventilation or ECMO. It is likely that inpatient and critical care would be prioritized given the desire to repurpose therapies in those settings.

The WG agreed that pragmatic trials of repurposed (but not investigational) compounds with simple endpoints could be launched in a month's time. For example, in a study of COVID-positive outpatients, a simple endpoint could be hospitalization. Such pragmatic trials could result in quick answers for large populations.

Inventory of Clinical Trial Network Capacities

The WG agreed to conduct electronic surveys to ascertain network and site capacity in a two-pronged approach. First, to reduce burden on individual sites, the WG will survey the network Coordinating Centers, which will have basic information about, for example, the sites' data systems, data standards, patient populations, and access to reading centers and drug distribution centers. Second, individual sites can be surveyed for more nuanced data, such as numbers of cases and catchment areas, which may not be recorded by the Coordinating Centers and may differ by site based on the evolving nature of the epidemic.

WG members suggested collecting the following information about a site's capacity: patient participants, data management, regulatory environment, labs, linkages to health department and community, and methods to ensure safety (more of an investigational drug concern).

Networks with a strong infrastructure could be leveraged for their technology and relationships with sites to collate the surveyed information into a central database, perhaps through a portal as a way to reduce reporting burden on single sites.

Fit for Purpose and Quick Launch

Many networks are already fit for purpose to conduct trials in certain settings (e.g., PCORnet in outpatient settings). Still others are well positioned to launch new trials quickly (e.g., NIAIDS HIV/AIDS network). The factors that can predict launch readiness are existing contractual agreements, common data structure, data coordinating center, history of working together in different settings, and regulatory support. The WG agreed that available networks and sites that are clearly identified as fit for purpose and capable of a rapid launch should be tapped to start clinical trials as soon as possible, especially trials of repurposed drugs. Because the health care system is already stressed, it will be important to minimize the number of extra steps that a site must take to comply.

Innovation

Traditional public health reporting structures might not provide sufficient or timely information for effective response. By contrast, some websites are innovatively scraping and aggregating

data from multiple sources to develop heat maps of COVID-19 prevalence (e.g., Maryland). While some people might question the validity of such data, this approach might be the best way to get a real-time picture of the disease spread. However, even innovative approaches to data collection may not adequately forecast the ebb and flow of the virus in waves for months to come. Therefore, rather than “chasing the epi,” the WG agreed that it should cast a wide net—that is, add every possible site to the inventory that is fit for purpose and then filter down as outbreaks occur.

The WG also agreed that electronic health records (EHRs) are highly preferable to case report forms (which are more prevalent in single sites) as a means to collect data. As an added benefit, EHRs would enable off-site monitoring, which would limit exposure of monitors, patients, and clinical staff to the coronavirus. Other innovations include leveraging (1) the LabCorp registry to identify COVID-positive and -negative (and mostly outpatient) people for recruitment into trials and (2) networks that use e-consent (aka, no-touch consent) and telemedicine to engage participants who are remote from sites with capacity. Importantly, FDA has expressed a willingness to be flexible in its requirements about review and validation of software used in COVID-19 clinical trials, which will be an important consideration for researchers designing trials.

Challenges Specific to COVID-19 Clinical Trials

The WG members highlighted the following challenges specific to conducting COVID-19 trials:

- It will be difficult to identify participants for prevention trials, because the United States still does not have reliable or widespread testing. There are known issues with false-positives and false-negatives.
- Even sites deemed appropriate (e.g., ICUs) may be too overwhelmed to conduct a trial.
- Some sites might require that PPE and other needed materials and supplies are physically provided to them—rather than accepting the funds needed to purchase them as a budget line item.

Next Steps

The WG decided to form four subgroups to facilitate rapid execution of activities.

- Clinical Trial Network Inventory sub-WG (Inventory of networks and known capabilities)
- Survey Development sub-WG (Development of survey(s) and identification of target(s))
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James Doroshow, MD, Director of the Division of Cancer Treatment and Diagnosis, National Cancer Institute
David Goff, MD, PhD, Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute
Jim King, MD, Senior Medical Officer, Biomedical Advanced Research and Development Authority
Michael Kurilla (Co-Chair), MD, PhD, Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)
Seema Nayak, MD, Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases
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Laura Resnansky, Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech
Badhri Srinivasan, Head, Global Development Operations, Novartis
Peter Stein, MD, Director of CDER's Office of New Drugs, Food and Drug Administration
Michael Vincent, MD, PhD, Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer
Janet Woodcock, MD, Director of the Center for Drug Evaluation and Research, Food and Drug Administration

INVITED PARTICIPANTS

Jintanat Ananworanich, MD, PhD, Bill & Melinda Gates Foundation
Francis Collins, MD, PhD, Director, NIH
Christine Colvis, PhD, Director, Drug Development Partnership Programs, NCATS
Kathrin Jansen, PhD, Senior Vice President and Head of Vaccines R&D, Pfizer
Ashley Parker, PhD, NIH Office of the Director, NIH
Sarah Read, MD, Deputy Director, Division of AIDS, NIAID, NIH
Laura Resnansky, Vice President, Global Head of Clinical Operations - Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Roche/Genentech

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer, Research Partnerships, Foundation for the NIH (FNIH)*

Rosa Alvarez, *Consultant, Deloitte*

Stephanie James, PhD, *Senior VP of Science, FNIH*

Joseph Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate VP of Science, FNIH*

Karen H. Tountas, PhD, *Scientific Program Manager, Science, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Nina Gonzalez, *Senior Manager, Deloitte*

Elizabeth Kim, *Senior Consultant, Deloitte*

Benjamin Stratton, *Senior Consultant, Deloitte*

Brett Tolman, *Manager, Deloitte*

Nancy Tuveson, MBA, *Writer, Rose Li and Associates, Inc.*

Jonathan Wachtel, *Manager, Deloitte*

Appendix B: Chat Transcript

From David Goff to Everyone 10:37

The 7 point ordinal scale could provide good outcomes for pragmatic trials

From Larry Corey to Everyone 10:42

The 2 NIAID prevention networks; the HVTN and the HPTN have done integrated trials and we have 45 US sites, 45 sub Saharan African sites and 20 South American sites all integrated with a common ability to conduct similar or complimentary trials.

From Larry Corey to Everyone 10:45

Is there an interest in reaching out to European

From David Goff to Everyone 10:45

Primary care practice-based research networks will be important to include. Some are funded by CDC, mostly through their prevention research centers program, others by NIH mostly through the CTSAs.

From Nayaksu to Everyone 11:04

Vendor considerations/innovations in the trials of new therapeutics context - consider remote monitoring capabilities

From David Goff to Everyone 11:11

Patient populations for master protocols could be considered in the context of the 7-point ordinal scale, adding out-patient/uninfected for prevention and vaccine trials.

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed viral stock production, the status of manuscript resubmission, updates from the *In Vivo* Strategy and Data Portal Implementation Subgroups, and the future of the Preclinical WG.

Action Items

- Dr. Menetski will share the final draft of the criteria for adding or changing the SARS-CoV-2 reference strain with the WG
- Dr. Menetski will also share notes from the Small Animal Model Best Practices for COVID-19 Research with Drs. Kanevsky and Lutz (Done)
- Ms. Jonson will work with the NIH Office of the Director and NCATS to promote the manuscripts and Data Portal in a joint effort upon publication
- Any WG members active on Twitter or other social media platforms are encouraged to share the Data Portal link and solicit feedback.
- The portal to submit potential NHP studies is being developed by NCATS and will become available end of next week (9/18). A notice will be distributed guiding all submissions to the online portal

(b) (4), (b) (5)

BEI is expanding two new cell lines for (b) (4), (b) (5) (from Dr. (b) (4), (b) (6)) and (b) (4), (b) (5). Moreover, (b) (4), (b) (5) from BEI's previous production runs are being sent to (b) (4) for a nonhuman primate (NHP) study and to Operation Warp Speed (OWS) for assessment of infectiousness in NHPs and for use in ongoing Phase 3 studies; (b) (4), (b) (5) Dr. (b) (4), (b) (6), (b) (5)

BEI exchanged (b) (4) from sequencing of the recent production runs with (b) (4) at (b) (4). Analysis with (b) (4) calling algorithm did not reveal any differences in sequencing results compared to BEI's sequencing. BEI will continue to exchange (b) (4) and will further exchange samples for a complete sequencing comparison.

Two epidemiologists positively reviewed the WG's criteria for adding or changing the SARS-CoV-2 reference strain. Dr. Joseph Menetski will share the final draft of these criteria with the WG; if there are no objections to the criteria, they will be posted to the NCATS OpenScience Data Portal without further discussion.

Manuscript Status

The authors of the Animal Model Landscape manuscript met to discuss reviewer comments on the manuscript. To address these comments, the authors will add a description of human disease in the introduction as well as use cases for different animal models to address different

aspects of the human disease. Dr. Judith Hewitt will send the revised manuscript to this group and resubmit the manuscript to *Cell Host & Microbe* on Friday, September 11. Any members of the WG with minor feedback on the manuscript can contact Dr. Hewitt.

Subgroup Updates

***In Vivo* Strategy Subgroup**

The National Primate Research Centers (NPRC) Operations Committee is continuing to refine details for SOPs to be used for studies across all NPRCs. Dr. Angela Birnbaum (NPRC Operations Committee) has developed a training module for quality assurance that is currently under consideration for adoption by all NPRCs.

The NIH has formed its COVID Expert Panel to approve NHP studies. A notice will be distributed guiding all submissions for that Expert Panel to an online portal that is being created with help from NCATS; this portal will be completed by the end of next week.

Best Practices for COVID-19 Research in Small Animal Models Subteam

The Subteam's contracted writer, Lucas Smalldon, is currently capturing information from the first two informational sessions that will provide background for the Best Practices for COVID-19 Research in Small Animal Models Field Guide. The Subteam will meet next on Friday, September 11 to discuss in-life and post-mortem components of the field guide. Dr. Menetski will share notes from the most recent Subteam meeting with Drs. Isis Kanevsky and Cat Lutz after this meeting.

Data Portal Implementation Subgroup

The Subgroup has collected usage metrics from the animal model summary pages on the NCATS OpenScience Data Portal to assess public engagement. Since the pages were posted in July, they have received approximately 2,000 "hits" without a concerted promotional effort, although no feedback has been received. These numbers are expected to rise with publication of the manuscripts in *Cell Host & Microbe*, and, upon their publication, Ms. Samantha Jonson will work with the NIH Office of the Director and NCATS to jointly promote the manuscripts and the Data Portal. Any WG members active on Twitter or other social media platforms are encouraged to share the Data Portal and solicit feedback.

Future Role of the Preclinical WG

The WG's initial remit included five categories of objectives:

Objective 1: Preclinical Resource Map

Objectives 2/3: Pandemic Response Framework

Objective 4: Prioritization

Objective 5: Data Sharing

At the end of September, the WG will have completed its first three objectives and will move into its maintenance phase for objectives 4 and 5. The WG discussed the lack of current data on

pathogenesis and long-term sequelae following COVID-19 infection, noting that such issues are especially difficult to study given limited resources and the current prioritization of research on treatments and countermeasures; however, research on pathogenesis and sequelae will only become more important as the population emerging from COVID-19 infection increases. Dr. Christine Colvis will raise this concern with the ACTIV Executive Committee in a meeting this afternoon. Regular meetings of the WG during the upcoming maintenance phase represent an opportunity for WG members to share new findings related to these topics that could inform ongoing compound prioritization and data sharing efforts.

Next Steps

Dr. Menetski will share the final draft of the criteria for adding or changing the SARS-CoV-2 reference strain with the WG. Dr. Menetski will also share notes from the most recent Best Practices for COVID-19 Research in Small Animal Models Subteam meeting with Drs. Kanevsky and Lutz after this meeting. Ms. Jonson will work with the NIH Office of the Director and NCATS to promote the manuscripts and Data Portal in a joint effort upon publication. Any WG members active on Twitter or other social media platforms are encouraged to share the Data Portal and solicit feedback.

Appendix A: Participants List

WORKING GROUP MEMBERS

Peter Adams, PhD, *Health Scientist, Project Officer, BARDA*

Ralph Baric, PhD, (not in attendance) *Dept. of Epidemiology and Dept. of Microbiology and Immunology, UNC Chapel Hill*

Kara Carter, PhD, (not in attendance) *Executive Vice President Infectious Disease, Evotec*

Marc Charette, PhD, *Division of Cardiovascular Diseases NIH, NHLBI*

Tomas Cihlar, PhD, (not in attendance) *VP, and Head of Virology, Gilead*

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Michael Diamond, MD, PhD, *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Ken Duncan, PhD, *Gates Foundation*

Prabhavathi Fernandes, PhD, *Retired, most recently led biotech Cempira and DarPharma*

Josh Fessel, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID*

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Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Stephen Mason, PhD, *Associate Research Fellow, Pfizer*

Frank Nestle, MD, (not in attendance) *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

Liz Ottinger, PhD, (not in attendance) *Project Manager, NCATS*

David Payne, PhD, DSc, (not in attendance) *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, (not in attendance) *Director, Center for Aerobiological Sciences, USAMRIID*

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Srinivas Rao, MBA, PhD, (not in attendance) *Global Head Translational In Vivo Models, Sanofi*

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Sheri Hild, PhD, *Program Director for the National Primate Research Centers (NPRCs) at Office of Research Infrastructure Programs, NIH*

Isis Kanevsky, PhD, *Unit Director, Pfizer*

FNIH STAFF

Joseph P. Menetski, PhD, *Associate VP, Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD, *Manager, Monitor, Deloitte*

Harrison Hawk, *Analyst, Deloitte*

Caroline Sferrazza, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From hildsa to Everyone: 10:24 AM

California NPRC will do a study in old diabetic monkeys when they bring their ABSL3 back online.

From Josh Fessel (NIH/NHLBI) to Everyone: 10:37 AM

How's our social media presence been?

From Josh Fessel (NIH/NHLBI) to Everyone: 10:37 AM

(There we go!)

From Christine Colvis to Everyone: 10:48 AM

<https://grants.nih.gov/grants/guide/rfa-files/RFA-TR-20-003.html>

From Prabha to Everyone: 10:48 AM

Please do keep track of the old diabetic monkey results/pathogenesis for us..Thank you. Prabha

From Josh Fessel (NIH/NHLBI) to Everyone: 10:50 AM

@Christine, thanks so much for posting that link!

From Josh Fessel (NIH/NHLBI) to Everyone: 10:52 AM

(b) (6)

From Tony Punturieri to Everyone: 10:53 AM

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7274228/>

From Josh Fessel (NIH/NHLBI) to Everyone: 10:54 AM

(b) (6)

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed viral stock production, the status of two recently submitted manuscripts, ACTIV strategy to accelerate Phase 1-ready agents into clinical trials, and updates from the *In Vivo* Strategy and Preclinical Network Implementation Subgroups.

Action Items

- Dr. Hewitt will speak with the editor of *Cell Host & Microbe* to ensure that the revisions to the Animal Model Landscape manuscript align with the journal's vision and will resubmit the manuscript by September 11.
- Dr. Young will invite Evotec's Head of Clinical to participate in future discussions regarding the acceleration of Phase 1-ready compounds into clinical trials
- Dr. (b) (4), (b) (6) will send (b) (4), (b) (5) cells to BEI (b) (4), (b) (5).

(b) (4)

BEI has completed (b) (4), (b) (5). The first of these runs was a (b) (4), (b) (5) produced in Dr. (b) (4), (b) (6) (b) (4), (b) (5).

. The other three runs were (b) (4), (b) (5).

); all three of these runs

(b) (4), (b) (5)

(b) (4), (b) (5)

(b) (4), (b) (6) will perform experiments to compare their virulence; previous infection (b) (4), (b) (5).

Although the BEI production runs (b) (4), (b) (5)

(b) (4) and NIAID sites have observed the same (b) (4), (b) (5).

BEI will also swap viral samples with other groups to compare sequencing results.

BEI will receive (b) (4), (b) (5) cells from the Centers for Disease Control (CDC) and (b) (4), (b) (5) cells from Dr. (b) (4), (b) (6) for future production runs. All current BEI stocks will be aliquoted and saved for potential use.

Manuscript Status

Dr. Kara Carter resubmitted the Pandemic Response SOP manuscript (for *in vitro* and *in vivo* studies) to *Cell Host & Microbe* last week and is awaiting feedback from the journal.

Dr. Judith Hewitt received feedback on the Animal Model Landscape manuscript last week. The manuscript authors met earlier this week to discuss reviewer comments; they will add at least one table to provide a more thorough description of how various animal models compare to human disease. Dr. Hewitt will speak directly with the editor of *Cell Host & Microbe* to ensure that revisions align with the journal's vision; she will resubmit the manuscript by September 11.

The WG discussed the benefits of compiling a “press package” to promote the publication of the *Cell Host & Microbe* manuscripts. This package would highlight the progress that ACTIV has made in COVID-19 research and may also solicit more submissions for preclinical and clinical agent prioritization.

Acceleration of Phase 1-ready Compounds into Clinical Trials

ACTIV is not currently supporting preclinical agents through Phase 1 clinical trials but it could leverage existing NIH/NIAID mechanisms:

(1) The Product development broad agency announcement (BAA) to support sponsors lacking funding to execute Phase I trials and (2) the Phase I Clinical Trial Units for Therapeutics that support the design, development, implementation, and conduct of Phase I clinical trials to support companies lacking the expertise in Phase 1 trials. Furthermore, for companies lacking expertise in clinical trials, NIAID offers Phase 1 clinical trials. Drs. John Young, Joseph Menetski, and Rosa Maria Alvarez met with Drs. Stacey Adam, Judith Hewitt and Sarah Read of the Therapeutics-Clinical WG to discuss how ACTIV can indirectly address this gap. Dr. Carter advised that Evotec's “Head of Clinical” would be interested in joining future discussions on this topic, and further noted that companies have been increasingly reluctant to perform Phase 1 studies in healthy volunteers, preferring to move directly into Phase 1b trials in patients.

Subgroup Updates

***In Vivo* Strategy Subgroup**

The NPRC Operations Committee is finalizing SOPs for experiments to be performed at NPRCs and is working with NIH to identify sites with assay-specific expertise and existing contracts to enable centralized testing (e.g., Dr. David Montefiori's lab at Duke will perform neutralizing antibody assays). The NHP Coordinating Center is projected to be established during October.

Best Practices for COVID-19 Research in Small Animal Models Subteam

The Subteam hosted three presenters in a session on Tuesday, September 1, and discussed best practices for viral experiments and various mouse models. The Subteam plans to hold at least two more sessions. A synthesis of information presented during these sessions will be prepared by contracted writer Lucas Smalldon to serve as a basis for the Best Practices for COVID-19

Research in Small Animal Model Field Guide. Draft summaries for all sessions should be completed by mid-September and will be shared with the WG.

Preclinical Network Implementation Subgroup

Agent prioritization reviewers will receive compound data weekly, on a specified day. Preclinical and clinical agents will be reviewed on alternating weeks. To address the concern around lead time for review, the team will be giving reviewers at least 2 business days and the weekend to review the compounds. To the extent possible, only agents that do not require a Confidential Data Agreement (CDA) for the data will be sent to reviewers.

Next Steps

Dr. (b) (4), (b) (6) will send (b) (4), (b) (5) cells to BEI (b) (4), (b) (5). Dr. Hewitt will speak with the editor of *Cell Host & Microbe* to ensure that the revisions to the Animal Model Landscape manuscript align with the journal's vision and will resubmit the manuscript by September 11. Dr. Young will invite Evotec's Head of Clinical to participate in future discussions regarding the acceleration of Phase 1-ready compounds into clinical trials.

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FNIH STAFF

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Harrison Hawk, *Senior Consultant, Deloitte*

Caroline Sferrazza, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From hildsa to Everyone: 10:28 AM

Publizing the good things ACTIV is doing needs to be made more apparent. It is not being seen.

From Nancy Haigwood to Everyone: 10:28 AM

Especially with the recent Atlantic online article about NHP resources that mentions ACTIV.

From Christine Colvis to Everyone: 11:04 AM

Thank you all. I need to get on another call

High-Level Meeting Summary

The Preclinical Working Group (WG) reviewed the Preclinical and Clinical compound survey, discussed the restructuring of its sub-WGs, and considered how to use clinical data to inform animal models.

Action Items

- Ben to work with Mariam Deacy to incorporate feedback into the Preclinical and Clinical Data Request Survey
- Working Group to review updated version of the survey
<https://redcap.ncats.nih.gov/redcap/surveys/index.php?s=DAE87WPTE7&>
- Dr. Parker to work with the WG chairs to develop a process for using the current NIH Covid-19 information portal to identify companies to add to the survey distribution list
- Christine to help identify individuals who can provide technical support to survey users who have questions or difficulties completing the survey

For further discussion

- Integration of emerging human clinical data will be discussed further during the next WG meeting

Online Preclinical and Clinical Data Request Survey

Dr. Benjamin Stratton reviewed the current version of the preclinical and clinical data request survey for COVID-19 therapeutics (e.g., antivirals, immunomodulators, neutralizing antibodies, and anticoagulants). The survey solicits information that the WG has identified as necessary for expert scientific panels to effectively prioritize these therapeutic compounds for preclinical or clinical testing. Requested information includes sponsor contact details, general compound characteristics (e.g., type of intervention, stage of development, agent class, mechanism of action, and summary of existing human data), and detailed compound information (e.g., toxicity and PK). The online form combines multiple choice and free response questions and adaptively prompts users to provide only relevant information based on the answers they provide. Users can also upload compound dose-dependency data and any supporting documents, such as research manuscripts.

The WG members suggested the following nine updates to the survey:

1. Several acronyms may not be readily understood by all users (e.g., “SQ”) and should therefore be spelled out.
2. “Stage of Overall Development” should be reworded as “Most advanced stage of development for any indication”.

3. When asked about a compound's pediatric use, responders should be able to freely explain their answer in more detail.
4. Users should be able to save their progress while completing the survey (i.e., enabling them to complete it across multiple sessions).
5. Users should be provided a navigation pane to inform them of their progress and allow them to skip ahead.
6. Survey instructions should include an estimate of approximate time to complete the survey.
7. "Minimum clinical lead stage, not HTS hits" should be reworded for clarity.
8. Upon survey completion, users should be emailed a receipt with a summary of their compound submission.
9. Survey completion metrics should be generated automatically and made available to ACTIV membership.
10. The question, "Can the drug be manufactured quickly to scale up for broad use?" should be reworded to ask whether the drug's development is already a "commercializable process."

Asset holders may skip any survey question and still have their compound considered for prioritization. The survey is not intended to be comprehensive (this would overburden applicants), but it provides enough information for prioritization purposes. The WG chairs aim to have a live version of the survey available for dissemination by the end of the week. The WG may also need to identify individuals who can provide technical support to survey users who have questions or difficulties completing the survey.

When ready, a link to the survey will be sent to 1) individuals who have contacted NIH about compound testing, 2) companies identified by NIH as having promising compounds, 3) asset-holders identified by the ACTIV Executive Committee and, 4) groups who submitted promising compound information to the existing NIH COVID-19 information portal (Dr. Ashely Parker will help the WG access information submitted via this portal).

Preclinical WG Restructuring

The WG plans to restructure by replacing the *In Vitro* Assay and Animal Model sub-WGs with four new sub-WGs focused on the following topics: 1) establishing a data/knowledge portal (i.e., the future state of data collection, access, and curation), 2) coordinating network of BSL3/4 sites for *in vitro* and *in vivo* non-NHP studies (e.g., funding sites and providing the research community with information on assays and site capabilities), 3) developing a process for preclinical agent prioritization, and 4) strategizing to implement compound testing in NHPs (e.g., generating a master protocol, prioritizing NHPs for testing, and determining funding requirements). The WG and sub-WGs will each meet once per week. Dr. John Young shared a slide detailing each new sub-WG's key activities, leadership, interdependencies (e.g., the preclinical prioritization sub-WG will need to liaise with the Clinical WG), and external dependencies (e.g., the NHP sub-WG will need to coordinate efforts with NPRCs).

This restructuring corresponds to the second phase of WG activities as they have advanced from identifying and inventorying information needed to respond to COVID-19 to disseminating compound and model information obtained during the first phase and implementing strategies

to execute compound testing. During main WG meetings, members will provide feedback and additional support to the sub-WGs and address any need for further sub-WG restructuring. Dr. Prabha Fernandes volunteered to fill the vacant Preclinical Agent Prioritization sub-WG leadership position, and Dr. Joseph Menetski recommended Dr. Michael Diamond (not on the call) as a potential second leader. Dr. Greg Gatto also volunteered to support this group.

Integration of Emerging Clinical Data into Animal Models

The WG must carefully consider how to leverage human clinical data, such as cytokine measures and transcriptomics, to design effective animal models to test candidate COVID-19 therapeutics. Dr. Jay Rappaport noted that although leveraging transcriptomics research may be relatively straightforward, leveraging cytokine measures will require defining specific platforms and identifying promising analytes. An additional challenge will be acquiring human tissue for preclinical work, which will require BSL3/4 facilities to perform autopsies—although some NPRCs also perform human autopsies because they have the protective measures to prevent contagion. Therefore, the WG may need to generate an inventory of BSL3/4 facilities capable of conducting autopsies and strategize with the Clinical WG regarding how to acquire human tissue for preclinical use.

Next Steps

Once updated with the recent WG feedback, WG members will be provided a link to the online data request survey and are encouraged to provide timely feedback to enable a prompt launch. Dr. Parker will work with the WG chairs to develop a process for using the current NIH Covid-19 information portal to identify companies to add to the survey distribution list. The WG and its four new sub-WGs will meet weekly, and integration of emerging human clinical data will be discussed further during the next WG meeting.

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M. Louise M. Pitt, PhD, *Science Advisor – USAMRIID / DoD*

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Peter Adams, PhD, *Project Officer, Contracting Officer's Technical Representative, Influenza Division, BARDA*

Christine M. Cutillo, M.M.C.i., *Special Assistant to the Director, NCATS*

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Sheri Hild, PhD, *Program Director for the National Primate Research Centers (NPRCs) at Office of Research Infrastructure Programs, NIH*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Felicia Qashu, PhD, *Program Officer at National Institutes of Health*

FNIH STAFF

Stacey Adam, PhD, *Science Program Manager at the Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

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Benjamin Stratton, PhD, *Senior Consultant, Deloitte*

David Frankowski, PhD, *Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

No activity in chat box occurred.

Action Items:

- Dr. Jay Rappaport will share a white paper to ACTIV leadership outlining the necessary responsibilities of an NPRC coordinating group.
- Joe will share the newest version of the therapy request form to the WG after making the changes discussed.
- Joe will send members the most recent WG animal model inventory.
- Dr. Srinivas Rao will lead the WG in developing IP protection strategies by generating a first draft of the topics that need to be addressed.
- Dr. Rappaport will share guidelines on how the NPRCs enable academic researchers to publish data derived from research that uses IP.

High-Level Meeting Summary

The Preclinical Working Group (WG) met to determine how to coordinate activities of the National Primate Research Centers (NPRCs), to review WG funding, and to finalize the preclinical data solicitation.

Coordinating NPRC Activities

Multiple NIH institutes (e.g., NIAID and NIA) and extramural researchers require access to limited nonhuman primates (NHPs) to develop vaccines and therapeutics for COVID-19. Dr. Jay Rappaport will provide a white paper to ACTIV leadership outlining the necessary responsibilities of an NPRC coordinating committee to better coordinate animal and facility use across all the NPRCs. The group will not only coordinate what studies are conducted across NPRCs but will also facilitate the initiation and publication of those studies. The coordinating committee will provide a single source of the virus and open access to documents such as master protocols, confidential disclosure agreements, and institutional animal care and use committee documentation. It will also support publication policies and maintain a data center that provides broad access to study results.

Funding for activities necessary to execute the Preclinical working group plan.

The WG will need to determine how much funding is needed to successfully identify and develop efficacious preclinical therapies for treating COVID-19 in the partnership and propose the budget to the Executive Committee. This proposed budget will (b) (4), (b) (5)

(b) (4), (b) (5)
The funding provided will need to be (b) (4), (b) (5)
a detailed description by the WG. The funding structure developed here may also be adapted by (b) (4), (b) (5)

Clinical/Preclinical Therapy Information Request Form

Dr. Joseph Menetski shared a Therapy Information Request Form with the group that will be used to solicit clinical and preclinical compound information from drug sponsors. The purpose of request form is to collect the requisite compound information to allow an expert panel to prioritize the most promising drugs for preclinical testing and to direct limited resources (e.g., NHPs) to them. The form will be accessible through a web link emailed to both academic and industry laboratories, research teams identified on BioCentury, and in response to inquiries sent to ACTIV. The form is being designed to balance the need for comprehensive data with the need to decrease the burden of providing it. To that end, the form combines multiple-choice answers and text boxes for detailed responses.

Information requested of applicants includes sponsor identification (which will be deidentified when sent to expert panels), general therapeutic information, a summary of the compound and its presumed target of action, SARS-CoV-2 related preclinical data, metabolic and pharmacokinetic details, safety data, tissue penetration, available clinical data, and drug availability/scalability. Preclinical data will be divided by antivirals, immunomodulators, other agents, and SARS-CoV-2 neutralizing antibodies. The SARS-CoV-2 neutralizing antibody section is in a preliminary stage and WG members are encouraged to add to it.

Dr. Menetski made changes to the form in response to WG member suggestions as the meeting progressed. The form will now collect information about the therapeutic intervention's stage of development so that only drugs in the 'clinical lead series phase' or further will be considered for prioritization. Other additions to the form include drug class (e.g., small molecule or biologic), viral source (e.g., from Wuhan or CDC), controls used in antiviral screening assays, dosage and route of administration in antiviral animal infection models, effect on related viruses, and stability and storage requirements (e.g., refrigeration). Route of drug clearance (i.e., renal or liver) was moved from the clinical section to the DMPK and PD section. Finally, the form will allow sponsors to attach supporting documents, such as published manuscripts.

Protecting Intellectual Property (IP)

The WG will collect proprietary information from pharmaceutical companies that submit compounds for prioritization in order to confirm the rigor and reproducibility of the research that generated the compound data. However, the need to share IP may dissuade some companies from submitting drug information. Therefore, the WG will protect IP by limiting the amount of data it provides when sharing compound data with the broader research community for drug comparisons. Dr. Srinivas Rao and others will assist the WG in implementing IP protection strategies and will coordinate with private companies to avoid problems related to data sharing. Dr. Rappaport is also creating guidelines on how to enable academic researchers to publish data derived from research that uses IP (e.g., allowing companies 30 days to review manuscripts prior to publication).

NCATS Open Science Data Portal

Group agreed that the ACTIV data capture system should leverage the NCATS Open Science Data Portal that was presented by Matt Hall of NCATS.

Next Steps

Dr. Menetski will make changes to the form and send it to the WG membership for input. The WG chairs intend to have the document finalized next week. Dr. Menetski will also send members the most recent WG animal model inventory.

Appendix A: Participants List

WORKING GROUP MEMBERS

Kara Carter, PhD, *Senior Vice President Infectious Disease, Evotec*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, *Virologist, Division of Antiviral Products, Office of New Drugs, FDA, CDER, DAV*

Prabhavathi Fernandes, PhD, *Retired*

Greg Gatto, PhD, *Drug Development Regulatory Project Leader at RTI*

Jay Grobler, PhD, *Executive Director, Infectious Disease and Vaccines Discovery, Preclinical, and Early Development (DPED), Merck Research Laboratories*

Judy Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research New Drugs, NIAID*

Samantha Jonson, MPS, *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Elizabeth Ottinger, PhD, *Project Manager, NCATS*

M. Louise M. Pitt, PhD, *Science Advisor – USAMRIID / DoD*

Srinivas Rao, MBA, PhD *Global Head, Translational In Vivo Models Global Research Platform, Sanofi.*

Jay Rappaport, PhD, *Director and Chief Academic Officer at Tulane Primate Center*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

INVITED PARTICIPANTS

Peter Adams, PhD, *Project Officer, Contracting Officer's Technical Representative, Influenza Division, BARDA*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

FNIH STAFF

Stacey Adam, PhD, *Science Program Manager at the Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD, *Senior Consultant, Monitor, Deloitte*

Brett Tolman, MA, *Strategy Manager at Deloitte*

David Frankowski, PhD, *Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

From Judy Hewitt to Everyone: 11:34 AM

I'd like to see route of administration in the therapeutic general section, rather than buried below.

From cat lutz to Everyone: 11:42 AM

maybe you need to emphasize the HUMAN data so you don't get folks filling in preclinical PK data

From (b) (6) to Everyone: 11:42 AM

I agree.

From John Young to Everyone: 11:43 AM

Yes, very important. Maybe we need to say HUMAN ONLY

Me = John

From Srinivas Rao to Everyone: 11:45 AM

agree Cat

From Kara Carter to Everyone: 11:46 AM

agreed

High-Level Meeting Summary

Action Items:

1. Working Group to provide feedback on the preclinical data prioritization form to finalize preclinical inputs on 5/15
2. Working Group to provide feedback on ACTIV-specific requirements for the Open Science Data Portal (Feedback will be captured in basecamp document or via email (to Joe or Rosa))
3. Working Group to provide feedback on Preclinical Strategic Vision slide (included in today's deck)
4. Working Group to suggest non-conflicted experts for the *in vivo* expert panel (e.g. from CROs or industry)
5. Working Group to suggest non-conflicted experts for the *in vitro* panel with anticoagulant and immunomodulator drug development expertise

The Preclinical Working Group (WG) met to discuss a newly developed NCATS Data Portal, as well as the WG's strategic objectives to accelerate compound testing and its criteria for therapy prioritization and immediate steps to begin rapid piloting of compounds.

NCATS Data Portal

Dr. Matt Hall shared a Data Portal being developed by the National Center for Advancing Translational Sciences (NCATS) to share COVID-19 therapeutic screening data and assay protocols with the broader scientific community. The Data Portal contains NCATS' pharmaceutical collection, which includes more than 2,500 approved drugs developed in Europe, the United States, and Japan, and approximately 6,000 other promising preclinical molecules that may lead to new therapeutic opportunities. Users can both view and download compound data and each compound has a unique identifier that can be readily adapted with the emergence of drug variants or new virus strains. The Data Portal also provides a modular user interface that allows multi-compound comparisons in a single view. In addition, dose response curves are provided for each compound and each therapeutic is linked to the NCATS Inxight database, which provides in-depth drug development data. Currently, the Data Portal only includes *in vitro* data, but it could potentially incorporate *in vivo* data as well.

The NCATS Data Portal is well positioned to serve as the WG's official platform for disseminating COVID-19 preclinical therapeutic data. With input from the WG, the Data Portal may further evolve to incorporate compound information from additional research sites (both public and private, including both positive and negative assay results) to allow for compound comparisons. Although some companies may be reluctant to provide data on proprietary compounds, NCATS can disseminate data to each user individually, based on their unique permissions. The Data Portal is tentatively scheduled to be launched next week.

Strategic Objectives to Accelerate Compound Testing

Dr. Joseph Menetski reviewed a slide listing these five long-term strategic objectives of the WG:

1. To generate a master inventory of the critical testing resources needed to support the generation of preclinical data.
2. To create a national strategy (including a master protocol) for using limited preclinical resources (e.g., non-human primates [NHPs]) during the crisis period of the pandemic.
3. To establish a virtual preclinical *in vitro* and *in vivo* testing network for therapeutic sponsors to access preferred or limited resources.
4. Establish standard protocols to support preclinical compound prioritization (including an expert review panel).
5. Create a public database for sharing of *in vitro* and *in vivo* model characteristics and data.

Achieving these objectives will allow the WG to accelerate therapeutic compound testing. The first step in this accelerated testing is to identify (1) therapies prioritized by the Therapeutics-Clinical WG, (2) preclinical compounds from existing databases (e.g., BioCentury), and (3) compounds submitted by sponsors. ACTIV would then review and prioritize the testing of these compounds. In addition to prioritizing agents for testing, ACTIV would recommend resources (e.g., NHPs) needed to test them. If testing yields promising results, the WG would use the data to recommend a therapeutic data package to the TX-Clinical WG for evaluation.

The WG has already assembled preliminary prioritization criteria and a list of expert panelists to oversee the prioritization process and has assembled inventories of BSL sites and their characteristics, animal model characteristics, and data on promising preclinical screening assays. However, other aspects of the prioritization process must still be established, including specific prioritization criteria (e.g., quantitative parameters of PK), a strategy for funding NHP centers, processes for prioritizing NHPs (e.g., African Green monkeys will likely be reserved for therapeutic studies and Rhesus Macaques for vaccine studies), and safeguards for protecting companies' intellectual property. Dr. John Young noted that the TX-Clinical WG has developed a compound prioritization strategy, and that the two WGs should liaise to harmonize efforts and minimize redundancy.

Preclinical Therapy Prioritization Criteria

Dr. Menetski shared a preliminary prioritization survey generated by Drs. Michael Diamond and Prabha Fernandes, which requires drug sponsors to provide compound information, including summary information on mechanism of action, existing human data, PK/PD, lung tissue penetration, and any applicable clinical data. This document was designed to provide an expert panel with all the information needed to prioritize compounds for testing. *However, the document requires immediate input from the WG to identify critical missing information and to provide feedback on type of quantitative metrics (e.g. specificity index description) associated with compound attributes.* Dr. Stacey Adam will also be providing feedback from the TX-Clinical WG regarding data necessary for drug prioritization. It is critical that this document request enough information to aid compound prioritization without overburdening applicants wanting

to submit compounds. The WG members should also suggest 'drop-down answers' to proposed survey questions to minimize the number of free text fields to simplify the review process.

Next Steps

The WG will receive the deck from today's meeting (inclusive of the strategic vision and preliminary preclinical therapy filtering Strategy), the deck from the NCATS Open Data Portal, and the data prioritization form and provide feedback by close of business Wednesday, May 13.. The preclinical prioritization process and the preclinical therapy prioritization survey will be finalized prior to our meeting on Friday May 15.

Appendix A: Participants List

WORKING GROUP MEMBERS

Kara Carter, PhD, *Senior Vice President Infectious Disease, Evotec*

Tomas Cihlar, PhD, *Vice President of Virology at Gilead Sciences*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Michael Diamond, MD, PhD, *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University School of Medicine*

Prabhavathi Fernandes, PhD, *Retired*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, National Institute of Allergy and Infectious Diseases (NIAID)*

Greg Gatto, PhD, *Drug Development Regulatory Project Leader at RTI*

Jay Grobler, PhD, *Executive Director, Infectious Disease and Vaccines Discovery, Preclinical, and Early Development (DPED), Merck Research Laboratories*

Judy Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research New Drugs, NIAID*

Samantha Jonson, MPS, *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Frank Nestle, MD, *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

Elizabeth Ottinger, PhD, *Project Manager, NCATS*

David Payne, PhD, DSc, *Vice President & Head, Medicine Opportunities Research Unit, GlaxoSmithKline*

M. Louise M. Pitt, PhD, *Science Advisor – USAMRIID / DoD*

Srinivas Rao, MBA, PhD *Global Head, Translational In Vivo Models Global Research Platform, Sanofi.*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

INVITED PARTICIPANTS

Peter Adams, PhD, *Project Officer, Contracting Officer's Technical Representative, Influenza Division, BARDA*

Ken Duncan, PhD, *Deputy Director, Discovery: Therapeutics, Bill and Melinda Gates Foundation*

Matthew Hall, PhD, *Division of Preclinical Innovation, NCATS*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Felicia Qashu, PhD, *Program Officer at National Institutes of Health*

FNIH STAFF

Stacey Adam, PhD, *Science Program Manager at the Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate Vice President, Science, FNIH*

Rosa Alvarez, PhD, *Senior Consultant, Monitor, Deloitte*

Benjamin Stratton, *Senior Consultant, Deloitte*

David Frankowski, PhD, *Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

From (b) (6) to Everyone: 02:07 PM

If audio gets messy, add questions to the chat.

From (b) (6) to Everyone: 02:18 PM

<https://drugs.ncats.io/>

From (b) (6) to Everyone: 02:45 PM

Thanks for the discussion of vaccines. One of the topics of discussion in the Vaccines WG is

(b) (5)

(b) (5) will undoubtedly be part of that. Thanks for all the consideration this group is putting into that topic.

From (b) (6) to Everyone: 02:55 PM

(b) (5), fully agree. (b) (5) - and that should be broken down by the species.

another parameter would be (b) (5) if relevant to the Therapeutic (and Vaccine)

Action Items:

1. Joe and Rosa to send the animal model inventory excel file to the Preclinical working group and to the leads of the Vaccine working group to review. ***Specific request: ensure that all the columns needed for prioritization and analysis are captured. (It is easier to take columns away versus adding them after we begin collecting data)***
2. The Preclinical WG is asked to provide any concerns about proposed members of the in vitro expert panel to Joe by this evening (***Saturday afternoon at the latest***). If no objections, then Joe will send a letter of invitation to join the ACTIV expert panel and begin to setup an initial meeting.
3. Michael Diamond will draft a 1-2-page preclinical asset review sheet (for expert panel review) before the end of the weekend [Note after meeting; Done]. Joe will send the draft to the Preclinical WG to provide additions from the animal model working group as well as anyone in the WG. This initial in vitro/ in vivo preclinical asset review sheet will be used as a starting point for the expert panels to modify. We will use this to begin setting up an input form for the needed data by potential sponsors.
4. Industry members of the working group will suggest people with CRO or industry experience but currently non-conflicted positions to the in vivo expert panel. These will be added to the NIH and academic suggestions by Dr Jim Anderson.
5. Jim Anderson and Chris Austin will work to obtain a view into all the NIH data in the publication portal supported by the office of portfolio management.
6. Joe will share the slide from Mike Diamond on the cross-subgroup information. [Done]

High-Level Meeting Summary

The Preclinical Working group (WG) met to discuss ramping up execution of ACTIV priorities, share the animal model inventory and *in vitro* expert panel list prepared by its subgroups (SGs), and address outstanding questions from the SGs. Drs. Christine Colvis and John Young relayed the ACTIV Leadership Group's desire to identify the best available nonhuman primate (NHP) models, evaluate how much effort is needed to validate models of interest, and determine which animal models could be used as prerequisites before testing a compound in NHPs.

For future reports to the Leadership Group, the WG will include appendices documenting its rationale behind specific recommendations, such as why certain compounds are prioritized over others. Future reports to the Leadership Group may also give equal attention to *in vitro*, small animal, and NHP testing. In addition, the WG has now been tasked with assessing therapeutics *and* prophylactics with potential relevance to COVID-19.

Study Initiation

Initiating NHP studies, once they have been prioritized, will require the WG to work closely with the national primate research centers (NPRCs). NPRC scientists offer extensive experience in NHP model validation and therefore should be included in WG discussions for joint decision-making; the WG should think of the NPRCs as partners.

NIH Institutes are being deluged with applications for COVID-19 grants, and studies involving NHPs have been halted to allow prioritization for COVID-19. Initiation of COVID-19 therapeutic and vaccine studies will require development of master protocols for *in vitro* and animal testing as well as guides for compound prioritization. Each NIH institute is only aware of the COVID-19 grants contained in its own portfolios—and each Institute has its own prioritization process. Therefore, ACTIV may need to create a group of NIH representatives with access to all grant portfolios to coordinate study prioritization of *in vitro*, small animal, and NHP studies across NIH institutes. Establishing a database of unfunded grants may also facilitate selection of future compounds for testing.

Initiating multiple waves of compound testing will require (1) identifying clinical stage molecules that require further preclinical support to be eligible for prioritization in NHP studies; (2) coordinating across NIH Institutes to help align their priorities with ACTIV; and (3) soliciting information on preclinical compounds in databases such as BioCentury to aid prioritization by an expert panel. It will also be crucial to understand what research is already being done to avoid duplication of efforts, and to find partners to collaborate with. Dr. James Anderson has offered access to a database of all publications and preprints on COVID-19 with related supplementary materials and grant applications (<https://icite.od.nih.gov/covid19/search/>, updated daily). Drs. Michael Diamond and Prabha Fernandes are also cataloguing the pharmacological properties of promising compounds to facilitate seamless and comprehensive comparison among drugs. The WG ultimately aims to build an automatic system to solicit requisite compound information from researchers before considering that compound for testing.

Animal Model Inventory

The Animal Model SG created an inventory that includes testing data from both small animals and NHPs and that delineates how to utilize each model, and it designing a strategy to keep this inventory updated. Dr. Cat Lutz agreed to maintain mouse model information, and Dr. Greg Gatto agreed to do the same for other small animals; a colleague of Dr. Judith Hewitt will be responsible for maintaining NHP information. The WG must also determine how to make the inventory accessible to the research community. Initially, this inventory did not include immune parameters of each model, which will need to be added. Dr. Hewitt asked for each WG member to suggest additional columns for the inventory and to identify any other omissions. The WG will also solicit feedback from the Vaccines and Therapeutics-Clinical WGs, intending to finalize a list of columns by the beginning of next week. An electronic form will populate the document to protect the integrity of the master list.

Expert Panel and Compound Prioritization Criteria

The *In Vitro* SG has generated a list of fourteen to fifteen experts to serve on an *In Vitro* Expert Panel to prioritize compounds for *in vitro* testing. The panel is half-composed of industry professionals (some retired) with success in progressing drug testing into clinical trials, and half-composed of academics with expertise in coronaviruses, drug screening, or both. Once panel membership is approved, official invitations will be circulated to nominees.

The *In Vitro* SG will also generate a list of criteria for agent prioritization (e.g., cytotoxicity, virus reduction assay data, and mechanisms of action), which will then be reviewed and revised by the *In Vitro* Expert Panel. Next, the WG will post these finalized criteria online where drug developers can then supply the requisite information about their drugs. The deidentified data will then be transmitted to the Expert Panel for unbiased prioritization. Although an initial Expert Panel has been identified for *in vitro* studies, an *In Vivo* Expert Panel will also be needed. For expediency, the WG may create a single online form for both *in vitro* and *in vivo* data, which will automatically direct applications to the appropriate review panel. All prioritization criteria must also be approved by the Therapeutics-Clinical and Vaccines WGs. Drs. Diamond and Fernandes will provide WG members with a list of sample criteria by the beginning of next week.

Assessing Immunomodulator Efficacy (b) (4)

(b) (4)

. Dr. (b) (4), (b) (6) presented a slide listing promising (b) (4)

(b) (4)

Next Steps

WG members will provide feedback on the animal model inventory, specifically by suggesting columns to be added and identifying critical data omissions. *In Vitro* Expert Panel members will be approved and the WG will begin assembling an Expert Panel for *in vivo* testing. Drs. Diamond and Fernandes will draft a list of compound prioritization criteria. As progress continues, the WG may also reorganize its subgroups based on emerging needs.

Appendix A: Participants List

WORKING GROUP MEMBERS

Annaliesa Anderson, PhD, Vice President and CSO Bacterial Vaccines, Pfizer

Kara Carter, PhD, Senior Vice President Infectious Disease, Evotec

Christine Colvis, PhD, Director, Drug Development Partnership Programs, NCATS

Michael Diamond, MD, PhD, Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University School of Medicine

Prabhavathi Fernandes, PhD, Retired

Greg Gatto, PhD, Drug Development Regulatory Project Leader at RTI

Jay Grobler, PhD, Executive Director, Infectious Disease and Vaccines Discovery, Preclinical, and Early Development (DPED), Merck Research Laboratories

Judy Hewitt, PhD, Deputy Director, Office of Biodefense, Research Resources and Translational Research New Drugs, NIAID

Samantha Jonson, MPS, Special Assistant to the Director, NCATS

Frank Nestle, MD, Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi

Elizabeth Ottinger, PhD, Project Manager, NCATS

Jay Rappaport, PhD, Director and Chief Academic Officer at Tulane Primate Center

John Young, PhD, Global Head Infectious Diseases and Early Development, Roche

Srinivas Rao, MBA, PhD Global Head, Translational In Vivo Models Global Research Platform, Sanofi.

INVITED PARTICIPANTS

James M. Anderson, M.D., Ph.D., Deputy Director for Program Coordination, Planning, and Strategic Initiatives, NIH

Christopher Austin, MD, Director, NCATS

Ken Duncan, PhD, Deputy Director, Discovery: Therapeutics, Bill and Melinda Gates Foundation

Eric Hughes, MD, PhD, Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis

Ashley Parker, PhD, Health Science Policy Analyst, NIH

FNIH STAFF

Joseph P. Menetski, PhD, Associate VP of Research Partnerships, FNIH

Michael Santos, PhD, Associate Vice President, Science, FNIH

Rosa Alvarez, PhD, Senior Consultant, Monitor, Deloitte

David Frankowski, PhD, Writer, Rose Li and Associates, Inc

Appendix B: Chat Transcript

From (b) (6) to Everyone: 11:25 AM

I think Dr (b) (6) was thinking very broadly and included model validation and disease pathogenesis.

From (b) (6) to Everyone: 11:27 AM

He does think broadly. I'm meeting with him later if anyone would like clarification

From (b) (6) to Everyone: 11:27 AM

That would be great. We didn't get to have an exchange during the meeting.

From (b) (6) to Everyone: 11:31 AM

Here was Dr (b) (6) comment: (b) (6) Can the team suggest what types of experiments would provide broader learnings just than single drug or vaccine? such as creating learnings cross many products"

From (b) (6) to Everyone: 11:32 AM

(b) (6), yes that would be great. I believe, appropriately so, the focus of ACTIV we are involved with have been toward a Therapeutic or Vaccine. Perhaps he is thinking more from a (b) (5) response characterization to infection etc etc. Makes sense to me. I bet many of the intra and extamural grants will be aimed at this as well. (b) (6)

From (b) (6) to Everyone: 11:36 AM

Considering different targets (eg viral vs. host and disease pathology targets , a one size fits all is not god. Since 2 or more drugs may be needed in therapy of these patients. For each of these targets we could come up with best profile.. (b) (6)

From (b) (6) to Everyone: 11:36 AM

I think the samples from the studies, that are not used, can be made available as part of a sample bank for further studies regarding the clinical and animal models and also defining better what is working and what isn't. It would be worth collecting samples for plasma and RNAseq etc. Such mechanistic information could help define synergies and combinations

From (b) (6) to Everyone: 11:38 AM

Animal studies - samples would be helpful. Human studies are not "pure" as all patients are getting more than one drug.. (b) (6)

High-Level Meeting Summary

The Therapeutics-Preclinical Working group (TX-Preclinical WG) planned for its report to ACTIV leadership next week. Dr. John Young also informed the WG that the Vaccines WG is interested in using animal models for vaccine development; therefore, the two WGs should work closely together to complement each other's efforts, avoid redundancy, and collaborate to prioritize therapeutics and vaccines for testing in animal models. Co-Chairs of each WG plan to attend the other WG's meetings, and participants also favored scheduling a separate meeting of both WGs to discuss immune enhancement—including methods of secondary infection, vaccination with specific antigens, and passive transfer of antibodies.

Action Items:

- Revise the slides for presentation at the Leadership Meeting. Joe and Rosa to revise, John and Christine to review.
- Prepare slides to describe the proposed NHP strategy for discussion with the NPRC directors on Tuesday, May 5th.
- Small animal team to complete the Table of small animal models and their preferred use for prioritization and presentation to this team next week.
- Send list of Bios for the In Vitro expert panel for review to the full working group, before sending meeting requests from FNIH and Co-chairs. [document included with these minutes, thank you Michael and Prabha for putting this together].

Prioritization Filter for Antiviral Molecules

The WG created a research pipeline with discrete research steps to help ACTIV prioritize both direct-acting and host-targeted antiviral compounds for further development. Dr. Jay Grobler reviewed in detail each step of the pipeline, which consisted of two main channels: (1) core research (Pandemic Response Mode) activities, which broadly address cellular efficacy, toxicity and pharmacokinetics, and (2) “non-gating” research activities, which broadly address secondary testing (e.g. resistance profiling).

The pipeline core activities begin with antiviral screening assays using a non-human cell line followed by secondary screening assays using a human cell line, both to assess compound cytotoxicity. After this, pharmacokinetics (PK) assays are run to support drug efficacy, followed by safety studies, and finally human clinical trials. Critically, if a compound already has enough safety data and promising preclinical PK data, it may move directly from secondary screening assays to human clinical trials.

The non-gating research for compounds in development will be conducted in parallel with the core research activities. For FDA approved compounds being repurposed, non-gating trials may be conducted in parallel with human clinical trials in order to further develop pharmacology models. Specifically, these non-gating studies include (but may not be limited to) assessing

information on SARS-CoV-2 viral load, target identification, target specific biochemical assays, resistance selection and profiling, expanded antiviral profiling, multi drug interactions, and efficacy in SARS-CoV2 (which may be transitioned to core activities when no longer in Pandemic Response Mode).

Participants further discussed how much detail to include when presenting the compound screening pipeline to ACTIV leadership. The team agreed that the overall testing progression would benefit scientists with expertise in virology and drug development, whereas details such as EC50 value suggestions would benefit academics and small companies. Researchers interested in advancing their compounds to clinical trials should be able to use the pipeline to understand how ACTIV has prioritized compounds (i.e., using what type and quality of data?). The team also agreed that the parameter values are recommendations, not requirements for progressing to clinical studies and may depend on other physiochemical properties.

The WG has also recommended the use of specific control compounds (e.g. (b) (4)) to allow researchers across the globe to establish similar baseline controls, thus promoting comparability of results.

(b) (5) **Strategy Decision** (b) (5)

The WG (b) (5), which Dr. (b) (6) presented in detail, that will inform scientists when a non-antiviral compound may be tested in (b) (5) whether that testing should occur in (b) (5)

Until August 2020, testing in (b) (5) will focus on validation studies of high priority *therapeutic* agents with available clinical data that target symptomatic and severe COVID-19 disease states. Alternatively, (b) (5)

. After August, requirements for testing in (b) (5)

This timeline for the (b) (5) could potentially change as new (b) (5) become available. The team suggested that the (b) (5)

Although (b) (5), because they have exhibited Acute Respiratory Distress Syndrome (ARDS) in response to SARS-CoV-2, their availability is limited. (b) (5)

Because of the overall limited (b) (5) which will coordinate the degree of study duplication (i.e., enough for rigor and reproducibility without wasting resources) and assist in repurposing existing projects and contracts. In the coming week, (b) (5) directors and chairs of the TX-Preclinical WG will be discussing a national strategy for coordinating resource use to maximize (b) (5) testing (b) (5) Level-3 and -4 facilities. They will also discuss how to expand the current infrastructure to provide resources necessary to combat future pandemics.

The WG will also solicit input from the (b) (5). To date, (b) (5) SARS-CoV-2—(b) (5). To develop an optimal experimental paradigm for the master protocols, researchers will need to compare data (b) (5). They must also determine optimal dosing. The master protocol may also include testing (b) (5) of investigative compounds both before and after SARS-CoV-2 infection.

Compounds being tested (b) (5) to help explain a compound's potential (or lack of) efficacy and interrogate the biological mechanisms of a drug in (b) (5).

Next Steps

The subgroups have assembled an inventory of promising small animal models—including information on their contexts of use—and are currently creating an *in vivo* and *in vitro* assay network to identify preferred assays for testing COVID-19-related compounds (to be discussed at a later meeting). Final adjustments will be made to the antiviral prioritization slide and (b) (5). (b) (5) will be revised to state that antivirals should not be tested (b) (5). A joint meeting with the Vaccines WG may also be scheduled in the future.

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Annaliesa Anderson, PhD, Vice President and CSO Bacterial Vaccines, Pfizer

Kara Carter, PhD, Senior Vice President Infectious Disease, Evotec

Christine Colvis, PhD, Director, Drug Development Partnership Programs, NCATS

Damon Deming, PhD, Virologist, Division of Antiviral Products, Office of New Drugs, FDA, CDER, DAV

Michael Diamond, MD, PhD, Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University School of Medicine

Prabhavathi Fernandes, PhD, Retired

Greg Gatto, PhD, Drug Development Regulatory Project Leader at RTI

Jay Grobler, PhD, Executive Director, Infectious Disease and Vaccines Discovery, Preclinical, and Early Development (DPED), Merck Research Laboratories

Judy Hewitt, PhD, Deputy Director, Office of Biodefense, Research Resources and Translational Research New Drugs, NIAID

Cat Lutz, PhD, Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory

Elizabeth Ottinger, PhD, Project Manager, NCATS

Jay Rappaport, PhD, Director and Chief Academic Officer at Tulane Primate Center

John Young, PhD, Global Head Infectious Diseases and Early Development, Roche

Srinivas Rao, MBA, PhD Global Head, Translational In Vivo Models Global Research Platform, Sanofi.

INVITED PARTICIPANTS

Peter Adams, PhD, Project Officer, Contracting Officer's Technical Representative, Influenza Division, BARDA

Ken Duncan, PhD, Deputy Director, Discovery: Therapeutics, Bill and Melinda Gates Foundation

Ashley Parker, PhD, Health Science Policy Analyst, NIH

Brett Tolman, MA, Strategy Manager at Deloitte

FNIH STAFF

Joseph P. Menetski, PhD, Associate VP of Research Partnerships, FNIH

Michael Santos, PhD, Associate Vice President, Science, FNIH

David Wholley, MPhil, Senior VP of Research Partnerships, FNIH

Rosa Alvarez, PhD, Senior Consultant, Monitor, Deloitte

David Frankowski, PhD, Writer, Rose Li and Associates, Inc

Appendix B: Chat Transcript

From Michael Santos to Everyone: 11:24 AM

To the points that are being made now: the primary initial objective of the Immune Enhancement sub-group is to review the existing relevant information, both from other pathogen experience (e.g., FI-RSV) and animal model and human observations with other CoVs. The people on the WG that have looked into this in some detail find a significant mix in the quality of studies that are cited. Hence a goal to provide a useful synthesis to inform vaccine development.

Also, for vaccine-associated immune enhancement, the Vaccines sub-group is drawing a distinction between ADE and cellular immunopathologies (with a perspective that these have at times been conflated in discussions).

From Kara Carter to Everyone: 11:24 AM

Thank you Mike.

From Christine Colvis to Everyone: 12:25 PM

I feel like we have what we need to present

Thank you for the great discussion

From John Young to Everyone: 12:26 PM

me too

From Michael Santos to Everyone: 12:29 PM

There is a meeting of the Vaccines Immune Enhancement Sub Group tomorrow morning at 10-11am ET. Clearly this is late notice, but if anyone would like to join that, you are welcome. Please contact Joe or me (Michael Santos).

And agree that this (and other animal model topics) are important for ongoing engagement between the Vaccines and Preclinical WGs.

From cat lutz to Everyone: 12:31 PM

great--thanks. I have to drop off

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard a presentation on NHLBI's COVID-19 efforts, including its involvement with ACTIV-4 trials and the Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (CONNECTS) Initiative.

NHLBI COVID-19 Efforts

Dr. Amy Patterson, NHLBI

Overview

COVID-19 has severe effects on the lungs, heart, blood and vasculature, which can lead to profound secondary effects on other organ systems (e.g., kidney, brain), and thus the National Heart, Lung, and Blood Institute (NHLBI) has launched multiple efforts to address the significant burden of COVID-19 on the respiratory and circulatory systems. NHLBI's main goal in relation to COVID-19 is to slow or halt COVID-19 progression and accelerate complete recovery by:

- Identifying host-directed therapies for COVID-19.
- Understanding short- and long-term trajectories of injury and underlying pathogenic mechanisms.
- Ensuring that COVID-19 clinical research findings are relevant and implementable, particularly for populations most severely affected.

NHLBI has developed a multidimensional approach, which executes activities focused on individuals and communities (i.e., clinical trials, long-term follow-up studies, and community engagement research), multiple therapeutic domains (i.e., passive immunity, immunomodulation, host tissue response, and anti-thrombotic), different patient settings (e.g., pre-hospital outpatient, hospitalized patients, and post-hospitalization convalescent patients), and multiple regions of the discovery continuum (e.g., developing biospecimen, data, and imaging repositories and analytics platforms and sharing data and samples among consortia).

Point of Care Diagnostics

NHLBI is testing some point of care (POC) diagnostics within clinical trials that have received FDA Emergency Use Authorization. These trials have a built-in two-tier testing approach with a 30-minute diagnostic test and later confirmatory testing.

NHLBI has worked closely with the National Institute of Biomedical Imaging and Bioengineering (NIBIB) on the Rapid Acceleration of Diagnostics (RADx) program, which includes a clinical studies core.

Host-Directed Therapeutics

NHLBI has launched or is supporting seven clinical trials, including ACTIV-3/4 trials. These trials are summarized below according to the trial's patient population.

- **Pre-Hospital Outpatient:** Colcorona, C3P0, and ACTIV-4B anticoagulation/anti-thrombo-inflammatory.
- **Hospitalized Patients:** ORCHID (HCQ), ACTIV-3 monoclonal antibody in collaboration with INSIGHT, and ACTIV-4A anticoagulation/anti-thrombo-inflammatory.
- **Post-Hospitalization Convalescent Patients:** ACTIV-4C anticoagulation/anti-thrombo-inflammatory.

Longitudinal Follow Up

NHLBI will soon launch a longitudinal/observational study called the COVID-19 Cohort of Cohorts for COVID-19 Research (C4R), which will aim to assess and understand the role of pulmonary, cardiovascular, and hematologic dysfunction in COVID-19 morbidity and mortality within diverse populations. This study will include multiple nested case-cohort studies, each with a standardized set of core examination and serologic assessments; depending on the specific patient population, additional measures may be added (e.g., multi-omics, spirometry).

C4R aims to accrue more than 70,000 participants and more than 15 cohort studies (largely those that are ongoing and have two or more clinical examinations, including a 10-year follow-up). The cohort studies selected have generated genotyping and deep phenotyping data (across multiple domains, such as imaging, biomarkers, social determinants, and lung function) on their highly diverse participants (in terms of age, geographic location, and representation of at-risk populations--e.g., those with pre-existing lung disease).

Community Engagement

NHLBI is involved in NIH-wide COVID-19 community engagement efforts, which aim to conduct community-engaged research and outreach focused on COVID-19 awareness and education in order to address misinformation and mistrust. These efforts led to the development of state-level Community Engagement Research Alliance Against COVID-19 in Disproportionately Affected Communities (CEAL) teams, which will promote and facilitate engagement of underrepresented racial and ethnic populations. Thus far, 11 CEAL team site locations have been identified according to rate of COVID-19 cases, access to underrepresented populations, and level of readiness to immediately engage with these populations.

CONNECTS Initiative

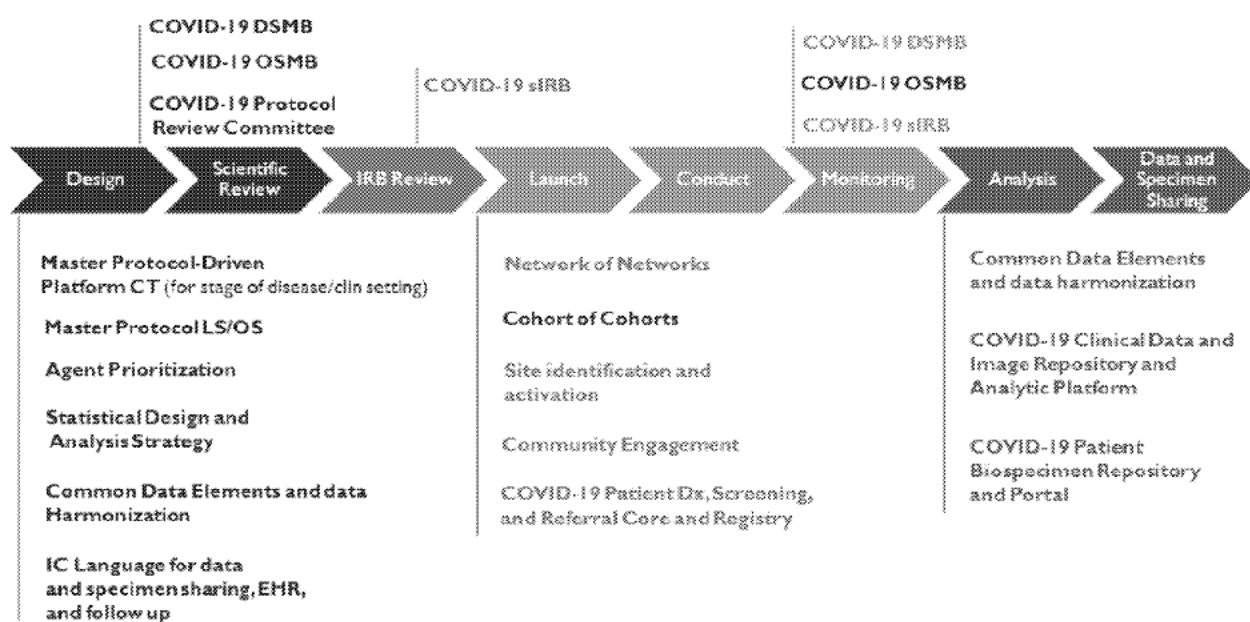
NHLBI launched the CONNECTS Initiative, which expands upon many of the ongoing NHLBI COVID-19 efforts outlined above and aims to fully integrate major NHLBI networks under one organizational system to ensure efficiencies, bandwidth, standardization, collaboration, and sharing of control groups, resources, and data. The CONNECTS Initiative actively collaborates with ACTIV, Operation Warp Speed (OWS), FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER), and Biomedical Advanced Research and Development Authority (BARDA).

The CONNECTS Initiative uses adaptive trial approaches with multiple, flexible active arms that can be quickly started/stopped as new data emerges and shift with the changing pandemic clinical landscape. It also aims to develop COVID-19 common data elements (CDEs) and to operate in a shared space with standardized repositories, imaging centers, and technologies.

The scope of the CONNECTS Initiative includes host-directed therapeutics clinical trials, longitudinal/observational studies, community engagement approaches, mechanistic studies, and data and biospecimen sharing.

The governance structure of the CONNECTS Initiative includes an Executive Committee and Steering Committee, with representation from NHLBI, NINDS, FDA, OWS, and BARDA, as well as master protocol teams, a trial oversight committee, a COVID-19 DSMB (also used as the ACTIV 4 DSMB), a Protocol Review Committee, and a single institutional review board (IRB). Each level of governance within the CONNECTS Initiative is connected in some way with OWS and ACTIV WGs or teams to ensure alignment of goals and strategy.

Dr. Patterson outlined the various activities and objectives of the CONNECTS Initiative at each stage of the COVID-19 clinical study lifecycle, shown below:



The CONNECTS Initiative's host-directed therapeutics master protocols will span from pre-hospital to post-hospital convalescence patient settings. The goal of these clinical trials is to identify promising therapeutic candidates that can mitigate COVID-19 impact on the heart, lung and blood. Thus far, the CONNECTS Initiative has received more than 60 agent recommendations from clinical scientists in the heart, lung, and blood research fields and these agents will require systemic and effective reviews as prioritization. Agent prioritization will be performed similarly to the ACTIV approach, in which members review a data package provided by an applicant company.

Discussion

C4R Studies

Participants requested additional information on the C4R study. Dr. Sean Coady noted that C4R is a combination of NHLBI consortia, including the Framingham Heart Study, ERIC-PPCI Study,

Jackson Heart Study, Multi-Ethnic Study of Atherosclerosis, Strong Heart Study, MASALA Study, Hispanic Community Health Study, and Cardia Study; lung-focused cohorts, like the COPD ROMICS cohort, Familiar Interstitial Program, Severe Asthma Research Program, and the CAPTURE Study cohort; and stroke-focused studies, such as the Northern Manhattan Study and REGARDS Study, through collaborations with NINDS. NHLBI will analyze these studies as one large cohort with COVID-19-focused objectives. Dr. Coady noted that C4R's protocols have been submitted and initiation of the study will be ready for launch soon because it will leverage existing infrastructure. The C4R Study will not result in de novo cohorts; however, some of the ongoing clinical trials, such as the ORCHID trial, may result in new longitudinal cohorts.

Co-Enrollment and Additional Clinical Trial Sites

Dr. LaVange inquired whether NHLBI has concerns related to participant co-enrollment in ACTIV trials. Dr. Patterson emphasized that the standard of care (SOC) for many COVID-19 clinical trials includes an anticoagulant agent and thus co-enrollment with ACTIV-4 trials (which is testing anti-coagulants) and other ACTIV trials is feasible and should not impact interpretability of results, as long as co-enrollment follows standardized procedures. Dr. Sam Bozzette noted that he has urged ACTIV-1 to consider co-enrollment with ACTIV-4, but the ACTIV-1 team is concerned that this combination will negatively impact interpretation of results. He also noted that issues related to co-enrollment will likely impede enrollment for NHLBI's post-hospital convalescent studies.

Dr. Judy Currier inquired on the development of new clinical trial sites within NHLBI's network. NHLBI currently has approximately 1,500 clinical trial sites, but aims to increase that number significantly to best facilitate all of its trials. Dr. Patterson noted that NHLBI is currently assessing the operational and logistical considerations related to new site development/opening and is discussing with RTI possible new clinical sites. Many sites with ongoing clinical trials are wary of incorporating additional trials because of concerns related to bandwidth, competition for resources or staff, and staff training requirements. Dr. Currier noted that certain clinical sites may be able to expand capacity by adopting a new site within their community that is not currently used for a clinical trial.

During a recent ACTIV-3 team discussion of co-enrollment and site capacity concerns, Dr. Francis Collins stated that ACTIV leadership is committed to encouraging sites to remain open to co-enrollment and conducting multiple trials. Dr. Collins also acknowledged common challenges related to regulatory differences between the U.S. and other countries, which can cause international ACTIV sites to experience considerable difficulties. Dr. Stacey Adam noted that Dr. Janet Woodcock of OWS will engage with international regulatory agencies to discuss these challenges and approaches to harmonize regulatory policies internationally.

Next Steps

Dr. Stacey Adam will distribute slides with status updates from the Master Protocol Subgroup (MPSG) regarding ACTIV-1/-2/-3/-4/-5 trials and information related to the multiple ACTIV TX-Clinical WG publications.

Dr. Currier will present during the next TX-Clinical WG meeting on the ACTIV-2 Public Relations Team's campaign to enhance patient enrollment and community engagement in ACTIV-2 trials.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)

John Beigel, MD, Associate Director for Clinical Research, Division of Microbiology & Infectious Diseases, NIAID

Sam Bozzette, MD, PhD, Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)

Timothy G. Buchman, MD, PhD, Biomedical Advanced Research and Development Authority (BARDA)

Judith Currier, MD, Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)

Ruxandra Draghia-Akli, MD, PhD, Global Head, Global Public Head R&D, Johnson & Johnson

Carl Garner, PhD, VP, Global Regulatory Affairs, Eli Lilly

Eric Hughes, MD, PhD, Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)

Andrei Kindzelski, MD, PhD, Program Director, Division of Blood Diseases and Resources, NHLBI

Lisa LaVange, PhD, Associate Chair, Department of Biostatistics, UNC

Elliott Levy, MD, Senior VP Global Development, Amgen; TransCelerate Board Member

John Mellors, MD, Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh

Naimish Patel, MD, Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi

Amanda Peppercorn, MD, Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)

Dionne Price, PhD, Director, Division of Biometrics IV, CDER, FDA

Michael Proschan, PhD, Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH

Sarah Read, MD, Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)

Yves Rosenberg, MD, MPH, Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI

Daniel Rubin, PhD, Division of Biometrics IV, CDER, FDA

Peter Stein, MD, Director of Office of New Drugs, CDER, FDA

INVITED PARTICIPANTS

Sean Coady, MA, Statistician, NHLBI

Christine Colvis, PhD, Director for Drug Development Partnership Programs, NCATS, NIH

Michelle Culp, MPH, Office of the Director, NIH

Ellen Gadbois, PhD, Office of Science Policy, Office of the Director, NIH

Mary Groesch, PhD, NHLBI

Jacqueline Kirchner, PhD, Senior Program Officer, Bill and Melinda Gates Foundation

Ashley Parker, PhD, Health Science Policy Analyst, NIH

Amy Patterson, MD, *Chief Science Advisor and Director of Scientific Research Programs, NHLBI*
Martha Petrovick

Tony Punturieri, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Ronald Reisler, MD, *Senior Clinical Advisor at David Defense Group, JPEO-CBRND-JPM CBRN Medical*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*

Allan Shipp, MHA, *Senior Clinical Research Policy Analyst, Office of Science Policy, NIH*

Christine Sizemore, PhD, *Director, Division of International Relations, Fogarty International Center, NIH*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Michael Santos, PhD, *Associate VP, Science, FNIH*

Evan Appell, *Consultant, Deloitte*

Helen Q. Chen, PhD, *Manager, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Stacey Adam to Everyone: 01:53 PM

Hi All, Given the discussion is going well. We will forego MP updates today.

Unless the MP teams object.

From Ruxandra Draghia-Akli to Everyone: 01:53 PM

Agree with you Stacey - very interesting presentation & discussion.

From Stacey Adam to Everyone: 01:55 PM

I will send out the slides for our general presentation and Amy's presentation after the meeting

If there are questions on the trials, please don't hesitate to reach out.

From Timothy G. Buchman to Everyone: 01:57 PM

Thanks so much! Great presentation.

From jacquelineki to Everyone: 02:00 PM

Amy: excellent presentation!

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard a summary of the recent Neutralizing Antibody (nAB) Scientific Summit, reviewed updates from the August 26 ACTIV Leadership Team meeting, and received status updates from both its Master Protocol and Agent Prioritization Subgroups (MPSG and APSG, respectively).

Neutralizing Antibody Scientific Summit

Drs. Francis Collins and Janet Woodcock hosted a Scientific Summit on August 20 focused on developing nAbs against COVID-19, which attracted more than 400 participants and provoked fruitful discussion. Dr. Stacey Adam presented a slide cataloging high-level takeaways from the summit that addressed learnings from studies of convalescent plasma and other fields as well as assay standardization, effector function and antibody optimization, epitope binding and viral resistance, and antibody-dependent enhancement. Draft white papers addressing these topics were provided to attendees before the Summit and are being refined based on the discussions that occurred there. Once these white papers are completed, Dr. Adam will distribute them to the TX-Clinical WG members.

Discussion

Dr. Adam will check on whether the nAb Scientific Summit was recorded so that WG members who were unable to attend can view it on demand.

Dr. Sarah Read highlighted the valuable learnings gleaned during the Summit from the field of Ebola, including discoveries that monotherapies appear to be as effective as cocktails, and that potent nAbs do not seem to require significant B-cell somatic mutation (which could suggest a need to ensure that clinical nAbs are sufficiently heterogeneous). The nAb Scientific Summit also led to discussions about the need to update assays as viral reference strains change; those involved in these discussions generally agreed that, for example, currently used assays should continue to be run against the Washington strain to avoid slowing testing, but that bridging studies should be conducted in parallel so that the qualified assays can be tested against the newer D614G SARS-CoV-2 strain.

ACTIV Leadership Team Meeting Update

During the August 26 Leadership Team meeting, Dr. Read clarified that FDA's recent Emergency Use Authorization (EUA) for convalescent plasma did not affect the urgent need for randomized clinical trials, and that consequently ACTIV's various master protocols, for now, should continue as planned. However, Dr. Woodcock noted that, particularly under ACTIV-3, patients may resist randomization to placebo, preferring instead to receive convalescent plasma as a treatment.

In addition to FDA's EUA, the TX-Clinical WG co-chairs also presented to the Leadership Team the new Big Effect Trial (BET or ACTIV-5) master protocol, which will provide inpatient Phase II testing of promising agents that lack sufficient clinical data to advance into a larger ACTIV trial. The Leadership Team approved of the TX-Clinical WG's plans to use BET to supplement its trials.

Dr. Collins also shared a two-by-two matrix that is still in development, with one axis cataloging patient populations and another cataloging various types of entities (e.g., vaccines and various therapeutic classes). Each cell, corresponding to an intersection of the axes, captures ongoing efforts in the relevant space (efforts are categorized as either [1] NIH-sponsored/planned trials, [2] ACTIV trials, or [3] ACTIV-associated trials). This resource will continue to be developed and will be shared once it has been stripped of all information deemed to be proprietary.

Discussion

Participants confirmed that ACTIV is not planning any convalescent plasma trials, because other groups, some of them sponsored by NIH, are already conducting such trials. Dr. Adam agreed to share Operation Warp Speed's (OWS's) progress reports on those trials with the TX-Clinical WG during future meetings.

Participants also confirmed that ACTIV's master protocols each establishes its own criterion for whether patients receiving convalescent plasma (i.e., because it is local standard of care) can be enrolled in those trials.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

The ACTIV-1 team received a second round of Pre-IND feedback from FDA on August 12 and is currently addressing both FDA's comments and comments received from its DSMB. The team has also finalized its Informed Consent Form, which it will submit to FDA as part of the master protocol's IND application. The team continues to liaise with NCATS' Trial Innovation Network (TIN), which will oversee ACTIV-1 operational planning/implementation; NCATS and company partners are preparing trial logistics. NCATS and (b) (4) have completed evaluating (b) (4) and have selected one to facilitate implementation of ACTIV-1; (b) (4) is now finalizing contracts with (b) (4). Next steps are to submit the ACTIV-1 IND application, complete (b) (4) contract negotiations, and continue planning operational logistics in anticipation of ACTIV-1 launch, which is expected to occur in early September.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

The ACTIV-2 master protocol launched on August 3, but as of August 27 it has only five active sites and (b) (4). The ACTIV-2 team and OWS leadership have been working to acquire additional rapid testing machines and kits, as well as mobile clinic options, for ACTIV-2 sites. The team has also been evaluating home health options and will soon finalize a contract with a chosen vendor. Next week, with support from the (b) (4), it will launch its new public relations campaign to raise awareness of the trial and increase patient participation. The team also continues to work with representatives from (b) (4) to incorporate their agents into the master protocol and has initiated preliminary conversations with (b) (4). Next steps are to activate additional sites, conduct the trial, and report regularly on the trial's status to ACTIV and OWS leadership.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

The ACTIV-3 master protocol launched on August 4, and as of August 26 has 10 open sites and (b) (4). The ACTIV-3 team and OWS leadership have collaborated to secure adequate supply of (b) (4) for the trial, enabling continuous activation of additional sites. The 20-patient DSMB Safety Review for (b) (4) is scheduled for August 31, and the team anticipates completing Stage 1 enrollment in September. The team continues to work with representatives of (b) (4) to incorporate their agents into the master protocol, and it has initiated similar conversations with (b) (4). Next steps are to activate additional sites, conduct the trial, and report regularly on the trial's status to ACTIV and OWS leadership.

Each week, Dr. Adam will now present site activation and patient enrollment statistics for both ACTIV-2 and ACTIV-3, which will include patient demographic breakdowns by gender, age, and ethnicity.

Discussion

Participants confirmed that the ACTIV-3 protocol allows sites to enroll patients even absent an adequate supply of remdesivir if needed (by replacing remdesivir with local standard of care). This option should help the ACTIV-3 team avoid serious delays that could otherwise be caused by limited (b) (4) supply, but the team strongly prefers to administer (b) (4) to all control subjects for consistency.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's pre-hospitalized and hospitalized protocols are approved for launch and will activate the week of August 24. Its post-hospitalized protocol is nearly finalized; the ACTIV-4 team must respond to DSMB comments and is still seeking drug supplies for this cohort. The ACTIV-4 trial will launch during the first week of September.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

The Phase II clinical information generated by this trial will help inform prioritization of agents for other trials including ACTT and ACTIV. The BET protocol is expected to launch during either the week of September 14 or 21; the first agents to be tested are risankizumab and lenzilumab, each against a shared placebo arm.

Discussion

Dr. Lisa LaVange and other participants highlighted the importance of establishing links among ACTIV WGs and the NHLBI/NINDS Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (CONNECTS) initiative to ensure alignment and avoid duplication or competition for patients.

Agent Prioritization Subgroup Updates

The APSG continues to prioritize agents, in parallel, across four classes: neutralizing antibodies (nAbs) and associated compounds, antivirals, immunomodulators, and symptomatic/supportive therapies (the latter three categories are being evaluated in concert with the Preclinical WG).

Neutralizing Antibodies and Associated Compounds

The ACTIV-2/-3 Agent Selection Committee (b) (4) and the Trial Oversight Committee (TOC) has approved (b) (4) of them (b) (4) to advance for clinical trial planning with the ACTIV-2/3 teams; these approvals are contingent on positive readouts from Phase I testing.

Discussion

In response to participant questions, Dr. Adam confirmed that independent confirmation of the neutralizing ability of candidate nAbs are still planned and will include retroactive confirmatory testing for nAbs already selected for entry into ACTIV-2/-3.

Antivirals

The Antivirals Subteam completed Wave 2 Assessment of 34 agents and the Agent Prioritization Review Committee (APRC) has reviewed the Subteam's recommendations. The Subteam is now following up with investigators on (b) (4) further evaluation and is also currently conducting (b) (4), (b) (5)

Immune Modulators

The Immune Modulators Subteam completed Wave 2 Assessment of 28 agents and the APRC has reviewed the Subteam's recommendations. The Subteam is following up with investigators (b) (4) for further evaluation, and it has also completed Wave 3 Assessment of 18 additional immune modulators and is awaiting APRC endorsements on its recommendations.

Symptomatic/Supportive Therapies

The Symptomatic/Supportive Therapies Subteam completed Wave 2 Assessment of 14 agents and the APRC has reviewed its recommendations. The Subteam is following up on (b) (4) for further evaluation.

Notes on Envisioned TX-Clinical WG Manuscripts

The TX-Clinical WG has previously discussed the possibility of drafting manuscripts to describe its agent prioritization and master protocol development processes, as well as lessons learned from these processes. Dr. Adam presented strawman outlines for these potential manuscripts and encouraged participants to review them before next week's WG meeting to help stimulate discussion. Dr. Adam also encouraged attendees to brainstorm potential ideas for an overall TX-Clinical WG paper, noting that such a paper could address higher-level issues than either of the two process-focused topics previously mentioned.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, NHLBI*

John Beigel, MD, *Associate Director for Clinical Research, Division of Microbiology & Infectious Diseases, NIAID*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI)*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

Elliott Levy, MD, *Senior VP Global Development, Amgen; TransCelerate Board Member*

Amanda Peppercorn, MD, *Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

Daniel Rubin, PhD, *Division of Biometrics IV, CDER, FDA*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, NCATS, NIH*

Mary Groesch, PhD, *NHLBI*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Allan Shipp, MHA, *Senior Clinical Research Policy Analyst, Office of Science Policy, NIH*

Christine Sizemore, PhD, *Director, Division of International Relations, Fogarty International Center, NIH*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Helen Q. Chen, PhD, *Manager, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Timothy G. Buchman: 15:59

The importance of RCTs needs to be echoed, repeated, and amplified both in the scientific community as well as among the public.

Lisa LaVange: 16:20

Agree!

Ruxandra Draghia-Akli: 16:37

Completely agree.

Timothy G. Buchman: 18:36

This messaging should be a focus for professional marketers. While we can make the case among ourselves, we are competing for attention and ultimately the "hearts and minds" of those fall ill and become candidates for trials.

Timothy G. Buchman: 25:56

Is the "PR campaign" professionally managed?

Timothy G. Buchman: 27:39

Excellent! This is so important. Tahnks!

Eric Hughes: 29:37

get message to subjects for a study whetheryou are tested positive or negative!

Eric Hughes: 30:06

great message...

Timothy G. Buchman: 35:08

The inclusiveness of the enrollment in national trials is so very important. Great news.

Currier, Judith, M.D.: 44:19

This is a great solution to integrate these efforts into ACTIV

Timothy G. Buchman: 44:26

So glad to see these plans for BET. This illustrates coordination among the outcomes of the evaluations by the review teams and direction of the agent to be tested to the most appropriate setting.

Neil Aggarwal: 49:01

Do we know how many more agents can be rolled into ACTIV-1?

Timothy G. Buchman: 51:57

That's a very useful "dynamic" figure. Looking forward to the distributable version.

Eric Hughes: 01:00:18



Christine Colvis: 01:00:48

The ACTIV process you guys set up looked REALLY good.

Ruxandra Draghia-Akli: 01:01:03

This is truly great.

David Wholley: 01:01:20

I agree that ACTIV was the star of the show at Faster Cures. Which means this group needs to PUBLISH on their accomplishments, including prioritization!

Christine Colvis: 01:01:35

Completely agree!

Ruxandra Draghia-Akli: 01:02:00

are the timelines for drafting these publications?

Christine Colvis: 01:02:01

There was no comparison

Currier, Judith, M.D.: 01:03:47

Great idea for the Stats publication

Timothy G. Buchman: 01:04:50

There needs to be a MS aimed for a much more general readership illustrating the foundational aspects of public/private/patient partnerships.

Timothy G. Buchman: 01:05:36

Even my clinical colleagues do not grasp the "why/what/how" of ACTIV.

Wednesday, September 2nd, 2020

Action Items

Action Items		
	Information	POC
1	Draft and send thank-you letter to the Deans (or other leads of the institutions) from Drs. Francis Collins and Janet Woodcock on behalf of the NIH and OWS to acknowledge the investigators and elevate the study with local leadership	Francis Collins/ACTIV PM Team/NIH OD
2	Draft a general thank you letter from Drs. Collins, Fauci, Gibbons, and Woodcock to the PIs for this study	Francis Collins/ACTIV PM Team/NIH OD
3	Draft a letter from Dr. Collins for junior faculty who may not be on publications for this effort to have in their file for when tenure discussions, etc. are had at their institution	Francis Collins/ACTIV PM Team/NIH OD
4	Review chatbox comments with updates from site investigators on key challenges or barriers	Francis Collins

Notes

Plenary Talk – Dr. Francis Collins

- Provided overview of the purpose of forming ACTIV back in April
- Discussed emphasis on ACTIV-3 recruiting efforts, recognized challenges sites faced
 - Some sites are also being asked to recruit for other trials – however, ideally Dr. Collins wants the ACTIV-3 trial to be prioritized
- Asked for site investigators to provide comments on what challenges they are facing
- *[See chat box for comments]*
- Peter Smith: They have champions at the sites, but receiving non-generic support from leadership (e.g., Deans of the Med School at the site) would be helpful
 - Idea to create a method of recognition / acknowledgement from Drs. Collins and Woodcock on behalf of the NIH for the young investigators supporting the studies
- Paola Lichtenberger (Miami VA): The VA isn't used to managing central IRBs, and they are also facing difficulty with competing trial priorities and declining numbers of cases
 - Letters from Drs. Collins and Woodcock with recognition / thank-you would help
 - Need additional support with informed consent and biosafety approval
- Wesley Self (Vanderbilt): The large academic centers have been approached by hundreds of studies - there could be great benefit in dividing up the trials across major academic centers across the world
 - Regarding ACTIV-3, the personnel and staff is a limiting factor – one idea is for the NIH to form a “mobile research expert team”

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- This team could help local research infrastructure to enroll quickly, as it's been difficult to enroll a large number of patients when a wave of COVID patients comes through
- Jason Baker (Minneapolis): Agreed with Peter Smith - a letter coming from Dr. Collins and the NIH would help elevate this trial with local leadership
 - It could also help to create a public awareness campaign about neutralizing antibodies as a potential treatment for COVID and the ACTIV-3 trial
- Jim Neaton: Also want to stress the importance of international collaboration required to complete these trials

Trial Status Updates

- Site Opening and Enrollment:
 - 18 sites activated, 13 sites open, and (b) (4)
 - Targeting 100 sites to be open by 9/21
 - Duke has 25, Baylor Scott has 23 (remainder can be seen in the presentation)
- Demographics:
 - Minor changes – slightly more males than females, and good distribution of ethnicity
- DSMB's Meeting on 8/31:
 - Encourage acceleration of site opening & recruitment
 - No safety concerns, but potential issue with drug-drug interactions
 - Next DSMB meeting scheduled for 9/21, need data captured by 9/15

Pioneer Site Updates

- Michael Bowdish (USC):
 - COVID hospitalization numbers have been slowly declining since July, with 4-8 admissions per day recently
 - Screened 50 patients in the past 7 days, 2 qualified and (b) (4)
 - Majority of their positive COVID patients are incidental. There is a large incarcerated population that would qualify for ACTIV-3 but are being missed
 - Rapid discharge program at USC posed a challenge for capturing qualifying patients in time
- Peter Smith (Duke):
 - Enrolling about 1 patient per day, and coordinating with hospitals nearby to capture more patients
 - Currently documenting how to manage this process
- Uriel Sandkovsky (Baylor, Scott, and White):
 - Seen a dramatic drop in cases over the weekend, but has increased over the past few days
 - No major issues with their 23 patients – 6 are admitted, and the other 17 are discharged and doing well
 - Difficulty overseeing staff managing these efforts, since they have other responsibilities

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- Milad Shareifpour (Emory):
 - 51 patients screened (b) (4), but facing issues with their census going down
 - Competing trials have been making it difficult to recruit patients
 - Anticipating a spike in cases with the upcoming Labor Day weekend
- Michael Matthay (UCSF):
 - (b) (4), but seeing lower number of patients overall
 - Hiring another coordinator to screen 7 days per week instead of 5
 - Hoping to set up an alliance with UCSF Fresno, since they have a large amount of COVID patients
- Clark Files (Wake Forest):
 - Cases are decreasing, but still seeing around 1-2 patients per day
 - Overall efforts are going well, currently have (b) (4)
- Wesley Self (Vanderbilt):
 - Protocol is going well, and no adverse effects from the infusion
 - Since last week, (b) (4) – both received infusion and have been discharged

Reporting of SAE

- Marc Teitelbaum provided an overview of the Standard AE (adverse event) Definition
 - Includes any abnormal signs, but there is some specific language around labs
 - Focused on clinical AEs – not focused on isolated labs that aren't associated with signs or symptoms
- Provided overview of approach to Isolated Labs
 - Medically important criterion must always be reasonably applied to any clinical finding / observation, including a lab
- Emphasized the need for everyone to be clear in their analysis – to ensure that events are appropriately categorized

Convalescent Plasma Follow-Up Discussion

- NIH recent statements have been very helpful, so that focus can remain on the trials

Next Steps

- Release of second newsletter coming soon
- Waiting for DSMB comments

Chatbox

From VHAMIAlightP to Everyone: 10:08 AM

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Me

Its (b) (6) from Miami VA

From (b) (6) to Everyone: 10:08 AM

I think the message is allocation of resources and efforts to focus on the trial

From (b) (6) to Everyone: 10:09 AM

I work at a safety net hospital with a high burden of COVID *but* very limited resources and limitation placed on use of hospital resources in terms of clinical trial operations

From (b) (6) to Everyone: 10:10 AM

Competing trials in the institution its definitely a limitation .

Cases trending down dramatically in our area (b) (6) although we are expecting cases to rise after reopening of schools and Labor day weekend in US

From (b) (6) to Everyone: 10:11 AM

Non RCT, RCT with inadequate sample size and RCT with low likelihood to impact mortality may be stopped?

From (b) (6) to Everyone: 10:12 AM

Hello. (b) (6) We have concerns about competing studies and prioritizing. My particular question is about ACTIV-4. I understand there is high level conversation about possible co-enrollment in ACTIV-3 and -4. I know this will be challenging. Where are these discussions and what are the possibilities?

From (b) (6) to Everyone: 10:14 AM

having (b) (5) is key.

From (b) (6) to Everyone: 10:14 AM

A letter to deans and site PI that not only asks (b) (5) but also as (b) (6) mentions, asks for Deans assistance (b) (5) —for instance most of the ACTIV3 teams are going to be very strong in inpatient, but (b) (5) of ACTIV3 would be very helpful

From (b) (6) to Everyone: 10:14 AM

CONGRATS, Miami!

From (b) (6) to Everyone: 10:15 AM

The issue is not only (b) (5) biosafety and data security perspectives

From (b) (6) to Everyone: 10:16 AM

I agree with (b) (6) :--we have had (b) (4) approval for over a week but are still working on (b) (5)

From (b) (6) to Everyone: 10:16 AM

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Capturing the importance of ACTIV-3 relative to other NIH/OWS-affiliated trials, as you mentioned in opening remarks, would be helpful. Multiple other studies are presenting priority letters and it is still difficult to navigate.

From (b) (6) to Everyone: 10:18 AM

Need for assistance with legal logistics with sponsors to enable more streamlined study conduct - allowing us/all (b) (4) to follow our policies and procedures for transporting vials to be on-site at participating Health-System pharmacies. This would increase ability to enroll in a more timely manner on weekends/holidays and off-hours

From (b) (6) to Everyone: 10:20 AM

I would love to have an infographic that I could share with patients, nurses, etc about the monoclonal antibody

From (b) (6) to Everyone: 10:22 AM

It would be great massive social media about monoclonal abx.. make it viral like convalescent plasma or the other medication.. that would help with patient awareness

From (b) (6) to Everyone: 10:22 AM

the complexities of documentation of informed consent across other languages is an ongoing problem even with the FDA relaxation.

From (b) (6) to Everyone: 10:23 AM

ACTIV-2 team is establishing rapid response teams, using military resources, to get sites assistance with physical resources. Also in talks with obtaining CRO resources, for selected site augmentation. There's an imminent site survey which is intended to identify where sites could use assistance

From (b) (6) to Everyone: 10:24 AM

thank you Dr Collins for your time!

From (b) (6) to Everyone: 10:24 AM

hi, (b) (6). all hospitals have different ways of prioritizing trials (i am involved in (b) (6)). a 'mandate' of sorts from the NIH level would certainly help sites make the case for preferentially enrolling the ACTIV-3 protocols over the others.

From (b) (6) to Everyone: 10:24 AM

Social Media outreach would be amazing, for patients and physicians/APPs/RNs alike. It would improve buy in from the rest of the teams providing care for the patients

From (b) (6) to Everyone: 10:24 AM

Considering the unpredictability of surges, a rapid response team approach may also be useful for ACTIV-3

From (b) (6) to Everyone: 10:28 AM

when can we enroll intubated patients ?

From (b) (6) to Everyone: 10:29 AM

Once we enter stage 2

From (b) (6) to Everyone: 10:29 AM

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after the (b) (4) (unless looks great even earlier)

From Adit Ginde to Everyone: 10:40 AM

Really important information from USC. With earlier discharges, the chance of readmission likely increases. This elevated the importance of the sustained recovery endpoint. Thanks for the hard work to make this possible!

From (b) (6) to Everyone: 10:42 AM

Agree Adit. Important also to share the various strategies of getting data/blood draws from patients at home. And you and Sam also raised the issue of patients discharged to nursing homes, which has its own challenges.

From (b) (6) to Everyone: 10:42 AM

One thing we can potential offer is to try to open ACTIV 3 at all LA County DHS facilities. This would more then double our exposure. Some logistical challenges to doing this, but this is something we are considering and I'm trying to start to work through.

From (b) (6) to Everyone: 10:44 AM

can we ask the question if race and ethnicity in the trial mirror the covid inpatient hospital census?

From (b) (6) to Everyone: 10:45 AM

a question from the NIAID div Dir meeting

From (b) (6) to Everyone: 10:58 AM

Regarding idea of (b) (4), (b) (5) - this is a great idea. (b) (4), (b) (5)

From (b) (6) to Everyone: 10:59 AM

Laura we already have the data from Duke on race and ethnicity re COVID patient census and will be forwarding to you.

From (b) (6) to Everyone: 11:00 AM

Our enrollment should mirror our race/ethnicity distribution very well (based on other covid trial enrollment)

High-Level Meeting Summary

Representatives of all ACTIV trial teams convened to receive trial status updates, hear a presentation on the design of ACTIV-6, and discuss FDA's response to ACTIV-2's proposed Phase III endpoints for non-infused agents.

Action Items

• Respond to email invitation to the Biospecimen Prioritization Committee	Trial Team Leads
• Contact Dr. Peter Stein to probe possibility of cross-trial conversation regarding trial endpoints	Stacey Adam
• Schedule a presentation from ACTIV-3B and update meeting agenda to include running review of assays	Stacey Adam

Trial Status Updates

ACTIV-1

ACTIV-1 has opened 44 sites (including 3 in Peru) (b) (4). The trial team expects to activate a significant number of additional sites in the coming week, despite declining hospitalization numbers. ACTIV-1 anticipates a DSMB review soon and has responded to FDA comments on Version 2 and its Statistical Analysis Plan.

ACTIV-2

ACTIV-2 has opened 112 sites (b) (4). Phase II enrollment of (b) (4) has finished and the agent is moving seamlessly into Phase III. Version 3 of the protocol is also open with (b) (4). (b) (4) was submitted to FDA on February 23. Due to difficulty transmitting virology data, the ACTIV-2 DSMB meeting has been delayed approximately two weeks to mid-March.

ACTIV-3

ACTIV-3 has opened 70 sites (b) (4). Its DSMB will meet on March 1 to assess the futility of (b) (4). (b) (4) is currently enrolling with an initial safety review scheduled for March 15. The trial is also planning onboarding of DARPins and a protease inhibitor in June after Phase I ascending dose data are available. ACTIV-3B/TESICO for sicker patients is being reviewed by FDA and safe-to-proceed is anticipated soon.

ACTIV-4

ACTIV-4A (hospitalized) has completed enrollment in the first phase of its trial, which supported the use of full prophylactic dose heparin in moderate hospitalized patients and low prophylactic dose heparin in patients requiring ICU care. A paper has been submitted to the New England Journal of Medicine and the team is working to open another trial arm by the end of February.

ACTIV-4B (pre-hospitalized) has opened 26 sites (b) (4). Its pilot low-touch enrollment pathway with (b) (4), with national roll-out

planned if successful. The trial's DSMB review has been scheduled for March.

ACTIV-4C (convalescent) has (b) (4). It is currently working to increase the number of sites, in part by enrolling discharged patients from ACTIV-4A.

ACTIV-5

ACTIV-5 has opened 17 sites (b) (4). A temporary pause in the lenzilumab arm, caused by manufacturing issues, was lifted by the IRB today. ACTIV-5 is assessing additional sites and investigational agents.

Biomarkers

Trial team leads suggested that cross-trial discussion of biomarkers and assays would help solidify the biomarker analysis process and ultimately aid in developing more sophisticated patient stratification and prognostic tools. Dr. Adam will incorporate into the monthly Cross-Trial Team meeting a running review of biomarkers/assays assessed and selected. She also agreed that the Biospecimen Prioritization Committee can offer feedback on assay selection and encouraged trial team leads to respond to the invitation to join that group.

Trial teams shared preliminary lists of assays under consideration:

- ACTIV-1: markers of inflammation (proteomic panels) and progression of cytokines
- ACTIV-2: anti-IFN antibodies, immune response panels, Vitamin D, and zinc
- ACTIV-3: antibody levels in plasma, D-dimer and CRP, viral load in nasal swabs, viral sequencing, soluble RAGE, and a 27-plex proteomics platform
- ACTIV-5: Olink

ACTIV-6 Synopsis

Drs. Adrian Hernandez and Susanna Naggie

ACTIV-6 will be an evidence generation system for oral outpatient drugs repurposed from other FDA indications that have an established safety record in humans and preliminary efficacy data for COVID-19. The study is a randomized, blinded, placebo-controlled Phase III trial with adaptive design, allowing the addition and removal of study drug arms and the alteration of randomization to leverage placebo data across arms. All study visits will be remote and endpoints will be assessed via online questionnaires. The study will enroll adults (at least 18 years of age) with confirmed SARS-CoV-2 infection and within 7 days of symptom onset, using standard exclusion criteria (e.g., allergy/sensitivity to components of study drug or placebo).

Endpoints and Power

ACTIV-6 aims to assess both symptom burden and the probability of changing clinical outcomes. The study's primary endpoint is symptom burden through Day 14, with hospitalization and death as the worst symptoms; if a drug shows significant benefit for symptom burden, the trial will assess whether it should continue on to further evaluation of clinical outcomes on the Modified COVID Ordinal Outcomes Scale. The trial's secondary endpoints are performance on the Outcomes Scale, hospitalization, and mortality through Day 28 as well as quality of life,

which is measured via the Patient-Reported Outcomes Measurement Information System (PROMIS) from baseline through Day 90. Exploratory endpoints include symptom occurrence, type, and severity. An estimated sample size of approximately 600 participants (per drug) will have 90% power to detect an odds ratio of 1.75 or greater (assuming a traditional proportional odds model and a type I error of .05).

Agents

The first agent to be tested in ACTIV-6 is ivermectin, a semi-synthetic oral agent—used primarily as an anti-parasitic—that is increasingly used globally to manage COVID-19. An Agent Prioritization Committee will meet shortly to finalize selection criteria and begin screening additional agents. Selection criteria will likely include a triage criterion requiring sufficient safety data to justify a low touch analysis and an efficacy assessment requiring positively trending but not definitive study results.

FDA Discussion of Symptom-based Endpoints

Dr. Davey Smith

ACTIV-2 met with FDA on February 11 to discuss endpoints for Phase III trials of non-infused agents. While IV agents are restricted to high-risk study participants and use an endpoint of hospitalization and death, non-infused agents are offered to “all comers” of high and low risk and do not have an established endpoint in the ACTIV-2 protocol.

Endpoint

ACTIV-2 Proposal

ACTIV-2 proposed a primary symptom-based endpoint for Phase III trials of non-infused agents, based on the rationale that all people with COVID-19 can benefit from treatment but that hospitalization and death endpoints are feasible only for very high-risk participants (requiring an estimated sample size of 5400 for an “all comers” population). To assess this endpoint, the team also proposed using diary-based, patient-reported outcomes (PRO), with a diary consistent with FDA guidance on symptom assessment for COVID-19 clinical trials.

FDA Response

FDA indicated (b) (5)

[REDACTED]

[REDACTED]

[REDACTED] To assess virology, FDA (b) (5)

[REDACTED]

[REDACTED]

at time of symptom release, if available; these data will be provided to FDA within 3 to 5 weeks.

Outcome Measure

ACTIV-2 Proposal

ACTIV-2 considered three outcome measures (all relative to the first of two consecutive days when the relevant measure is met): (1) time to confirmed absence of all targeted symptoms; (2)

time to confirmed alleviation of all targeted symptoms to a score of mild or absent; and (3) time to confirmed improvement in all targeted symptoms (i.e., time when all symptoms that were scored moderate or severe on Day 0 are scored mild or absent *and* when all symptoms that were scored mild or absent on Day 0 have become or remain absent). The final measure—time to confirmed improvement in all targeted symptoms—was proposed to FDA. Internal validity was assessed through correlation with global assessment questions (.46 correlation with time to overall COVID-19 improvement and .44 with time to return to health), and Kaplan-Meier curves largely matched across varying time thresholds for symptom resolution (for number of consecutive days equaling 1 to 4). ACTIV-2 proposed an effect size of 25% decrease in median time to symptom improvement, which is comparable to influenza treatment trials.

FDA Response

FDA asked ACTIV-2 to consider a (b) (5). Discussions continue over whether patients with these symptoms would consider themselves (b) (5). FDA also recommended (b) (5). However, the ACTIV-2 team has argued that (b) (5) who are already later in the disease course and would require subjective (b) (5) plans (b) (5).

Discussion

(b) (6) noted that time (b) (5). Requests for this outcome measure may come from FDA divisions that typically work on chronic disease—for which (b) (5) is appropriate—but that are currently reviewing COVID-19 trial protocols; for example, the Rheumatology division is reviewing ACTIV-2 (b) (6) noted in the (b) (5) could help facilitate conversation and address this issue. (b) (6) agreed to raise the issue with FDA contacts.

(b) (6) clarified that ACTIV-2 participants (b) (5). The team expects to launch an (b) (5) next week, following (b) (5) implementation issues. (b) (6) encouraged any other trials considering (b) (5) to use the ACTIV-2 platform as a starting point.

Symptom Duration Inclusion Criteria

Based on bamlanivimab data, FDA asked ACTIV-2 to provide a rationale for beginning study treatment sooner than 10 days from self-reported onset of COVID-19-related symptoms; ACTIV-2 has proposed to reduce that time period to 8 days.

Appendix A: Participants List

TRIAL TEAM MEMBERS

ACTIV-1

William G. Powderly, MD, *ACTIV-1 Chair and J. William Campbell Professor of Medicine, Director of the Institute for Clinical and Translational Sciences, Washington University in St. Louis*

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Lisa LaVange, PhD, *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Cynthia Boucher, MS, *Clinical Trials Specialist, NCATS*

ACTIV-2

David (Davey) Smith, MD, *ACTIV-2 Chair Professor of Medicine, U. California, San Diego*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Cyrus Javan, MD, MPH, *Medical Officer/Program Officer, Division of AIDS, NIH*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS, NIAID*

ACTIV-3

James D. Neaton, PhD, *ACTIV-3 Chair and Professor of Biostatistics, University of Minnesota*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen*

Birgit Grund, PhD, *Associate Professor of Statistics, University of Minnesota*

ACTIV-4

Paul Ridker, MD, *ACTIV-4B Chair; Senior Physician, Brigham and Women's Hospital; Eugene Braunwald Professor of Medicine, Harvard Medical School*

Tom Ortel, MD, PhD, *ACTIV-4C Chair and Chief, Division of Hematology, Department of Medicine, Duke University*

Scott Berry, PhD, *Adjunct Professor, Department of Biostatistics & Data Science, Kansas University Medical Center*

Jean Connors, MD, *Associate Professor, Department of Medicine Brigham and Women's Hospital*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI, NIH*

Eric Leifer, PhD, *Mathematical Statistician, NHLBI, NIH*

Allison Morris, MD, *ACTIV-4D Co-Chair and Professor of Medicine, Immunology, and Clinical and Translational Research, University of Pittsburgh*

Clinton B. Wright, MD, *Director, Division of Clinical Research, National Institute of Neurological Diseases and Stroke (NINDS), NIH*

ACTIV-5

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases*

OPERATION WARP SPEED

William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*

Gilbert “Lynn” Marks, MD, *Senior Adviser to BARDA, Office of the Director*

Col. Deydre Teyhen, DPT, PhD, *Director of Therapeutics, Operation Warp Speed*

TX-CLINICAL WORKING GROUP

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-Chair)*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

OTHER INVITED ATTENDEES

Kevin Bugin, PhD, *Director of Special Programs Staff, Office of New Drugs, Food and Drug Administration (FDA)*

Krishna Deepak, MS, *Consultant, Boston Consulting Group*

Nancy Geller, PhD, *Director, NHLBI Office of Biostatistics Research, NIH*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID, NIH*

Raahul Ramakrishnan, MD, *Project Leader, Boston Consulting Group*

Nada Saleh, MS, *Clinical Trials Specialist, Social and Scientific Systems*

Austin Van Grack, MS, *Committee Coordinator, Social and Scientific Systems*

David Wholley, MPhil, *Senior Vice President of Research Partnerships, FNIH*

STAFF

Evan Appell, *Consultant, Deloitte*

Alex Sorosa, *Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Kevin to Everyone: 01:13:17

They (OND) still meet everyday (across the divisions). But its challenging to resolve case by case. Especially, when their stats colleagues are not within OND. I think a dedicated discussion for CDER would be helpful.

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) received status updates on the ACTIV-2 and ACTIV-3 trials, discussed other topics elevated for its consideration, and reviewed statuses of ACTIV-6 and ACTIV-3b. The TOC also endorsed converting ACTIV-2 to an active control trial.

Trial Accrual and Status Updates

ACTIV-2

ACTIV-2 has activated 110 sites (b) (4). Phase 2 arm has reached its enrollment milestone of 220 patients; the AstraZeneca IV/IM arms, as well as the Camostat and Synairgen arms, have all achieved first patient in (FPI). The ACTIV-2 team plans to proceed with Brio Bio's agent without a pause pending the DSMB's safety review (virology data will then be used to establish graduation rules). Version 4 of ACTIV-2, which will test SAB's polyclonal Ab, was submitted to FDA on February 23.

ACTIV-3

ACTIV-3 has activated 52 sites (b) (4). Phase 2 arm has surpassed its target of (b) (4) and the ACTIV-3 team is preparing for the DSMB review of that arm, to occur on Monday, March 1. (b) (4), and the DSMB review is planned for March 15. The ACTIV-3 team is activating sites in Denmark, India, and the United Kingdom, and is also working to onboard the Molecular Partners agent—although supply issues might delay activation of the Molecular Partners arm if ACTIV-3 needs to wait until commercial stock becomes available in June. Dr. James Neaton noted that companies may sometimes overestimate drug supply at the outset of a trial, only to discover logistical hurdles once the trial launches.

Topics for Discussion

Delays in (b) (4)

Activation of ex-U.S. sites is significantly delayed for (b) (4) agent. (b) (4) declined to share its (b) (4) with ACTIV and stated that it would submit (b) (4).

However, (b) (4)

. Dr. (b) (6) will draft an email escalating these issues to (b) (4) senior leadership and send it to Dr. (b) (6) for his review. If the finalized email receives no response from (b) (4) then Dr. (b) (6) will escalate this issue within ACTIV leadership. ACTIV representatives may need to explain to (b) (4) representatives that, (b) (4)

(b) (4) Before Entering ACTIV-2 Phase 3

(b) (4) has proposed to (b) (4). The TOC agreed that the (b) (4) conform to ACTIV-2 study design.

(b) (4) /ACTIV-2 of FDA Variant Testing Requirements

FDA has (b) (5). Dr. (b) (6) emphasized that ACTIV-2 selected (b) (4) monoclonal Ab because of its novel dose formulation, and that a plan is needed to pair it with another Ab to comply with FDA's advisement. Dr. (b) (6) noted that (b) (4); Dr. (b) (6) noted that (b) (4) will soon send data to Dr. (b) (6) to inform the Ab matching. Once a specific pairing is proposed, Dr. (b) (6) will solicit approval from the selected company. This same process can be offered to any company. All companies submitting monoclonal Abs for ACTIV trials from this point forward will be apprised of FDA's new advisement.

Dr. (b) (6) asked whether (b) (4) needs to be matched with another inhaled Ab, in particular. Dr. (b) (6) noted (b) (4).

Dr. (b) (6) noted that, in light of this situation, the ACTIV-2 team is seeking the TOC's guidance on whether it should proceed with, or drop, (b) (4). Dr. (b) (6) noted a third option would be to wait for (b) (4) to provide data from tests of their Ab against SARS-CoV-2 variants of concern (pseudovirus data should be available within 1 week; live virus data within the next 2 weeks).

The TOC agreed to delay entering (b) (4) into ACTIV-2 until data on its neutralization of SARS-CoV-2 variants of concern become available in the coming weeks. Dr. (b) (6) will solicit weekly updates from Dr. (b) (6) on the status of these data.

The TOC also acknowledged that, by making this decision, (b) (5).

Potential Conversion of ACTIV-2 to an Active Control Trial

NIH has updated its guidelines to support the use of the Lilly Ab combination, so the ACTIV-2 team is asking the TOC whether it should convert to an active comparator for high-risk patients, and whether single agent bamlanivimab (BAM) could suffice as an active comparator. Dr. Smith noted that converting ACTIV-2 to an active control trial would transform it into a noninferiority design, which would require approximately 2,000 participants. Dr. Adam noted that the Lilly Ab combination is not being produced at scale (i.e., ACTIV-2 would be wholly reliant on USG supply of drug), whereas back stocks of BAM are available now. Dr. Lane proposed using local standard of care as active comparator and addressing resulting variability by adjusting the analysis plan.

The TOC generally endorsed the conversion of ACTIV-2 to an active control trial. The ACTIV-2 team will develop a specific proposal for implementing this conversion—perhaps consulting Dr. James Neaton to glean insights from the IV/IG trial design—and will then present it to the TOC.

Updates on Status of ACTIV-6

The ACTIV-6 protocol team has been meeting regularly to develop its trial design (e.g., selecting primary versus secondary endpoints with FDA input), secure its funding, and schedule a pre-IND meeting with FDA as soon as possible. The ACTIV-6 protocol team expects to have a completed trial design with fully secured funding during the first week of March. Once funding is secured, the protocol leads and representatives from the trial sponsors (PCORI and NCATS) will begin to attend the weekly TOC meetings.

Updates on Status of ACTIV-3b

FDA recently requested that ACTIV-3b be updated to include what the ACTIV-3 team regarded as infeasible safety parameters (e.g., daily vital signs, daily labs, and daily adverse events during hospitalization). The ACTIV-3 team drafted and submitted a response to FDA's request offering a compromise intended to preserve trial safety and feasibility and is waiting for the FDA reply.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Samuel Bozzette, MD, PhD, Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)

Kevin Bugin, PhD, Director of Special Programs Staff, Office of New Drugs, Food and Drug Administration (FDA)

Elizabeth Church, PhD, Deputy Director, Therapeutics Research Program, Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), NIH

Judith Currier, MD, Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)

Ann Eakin, PhD, Senior Scientific Officer, Concept Acceleration Program, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)

Emily Erbeling, MD, MPH, Director, Division of Microbiology and Infectious Diseases, NIAID, NIH

William Erhardt, MD, Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, Global Health Science Advisor, NIAID, NIH

James P. Kiley, PhD, Director, Division of Lung Diseases, NHLBI, NIH

Peter Kim, MD, Director, Therapeutics Research Program, Division of AIDS (DAIDS), NIAID, NIH

H. Clifford Lane, MD, Deputy Director for Clinical Research and Special Projects, NIAID, NIH

Jens D. Lundgren, MD, Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT

Gilbert (Lynn) Marks, MD, Senior Adviser to BARDA, Office of the Director

James D. Neaton, PhD, ACTIV-3 Chair and Professor of Biostatistics, University of Minnesota

Sarah Read, MD, Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)

Erica Ollmann Saphire, PhD, Professor, La Jolla Institute for Immunology

David (Davey) Smith, MD, Professor of Medicine, U. California, San Diego

Peter Stein, MD, Director of Office of New Drugs, CDER, FDA

OTHER INVITED ATTENDEES

Ashley Parker, PhD, Health Science Policy Analyst, NIH

STAFF

Stacey Adam, PhD, Director, Cancer, Foundation for the NIH (FNIH)

David Wholley, MPhil, Senior Vice President of Research Partnerships, FNIH

Helen Q. Chen, Consultant, Deloitte

Evan Appell, Consultant, Deloitte

Lucas Smalldon, MA, Writer, Rose Li and Associates, Inc.

Appendix B: Chat Transcript

(b) (6) 11:49

Hi (b) (6). I must have missed your email. You want a (b) (5)
(b) (6) I have the spreadsheet for the raw data if you want.

(b) (6) : 20:33

BUT if we did we will not have an agent in the trial if neither of our current agents move forward we won't have an agent in the trial Not ideal

(b) (6) : 20:49

Need to accelerate (b) (4)

(b) (6) : 22:02

indeed (b) (6) : intro meeting with (b) (4) tomorrow - so please help to push them (b) (6)

(b) (6) : 26:20

We will do our best to push quickly. I think (b) (4) will be ready to go.

(b) (6) : 28:56

Were I you, I would pause

(b) (6) : 29:40

Pause is important

(b) (6) : 30:04

agree w pause

(b) (6) : 30:16

agree, pause both

(b) (6) 31:15

Thanks very much!

(b) (6) : 33:28

(b) (5) companies who are interested in finding a complementary antibody.

(b) (6) : 35:09

(b) (6) can you share data relating to ongoing (b) (5) for various variants ?

(b) (6) : 35:46

Not sure if it was ACTIV 2 or ACTIV 3 but AZ has agreed to participate beyond just the LVNA

(b) (6) : 37:46

(b) (6) s - Yes, by footprint/binding community. The USG effort has a few more of the therapeutic candidates in action.

(b) (6) : 38:31

agree w (b) (6)

(b) (6) 38:42

and (b) (6)

(b) (6) : 39:02

agree

(b) (6) : 39:06

agree

(b) (6) : 55:32

i heard there were issues with (b) (5) if there is time can we hear the problems or are they not serious?

ACTIV, Therapeutics-Clinical Agent Prioritization Subgroup,
Wave 2 Preclinical/Clinical Antivirals Prioritization, Meeting Minutes

Thursday, July 2nd, 2020

Action Items

Action Items		
	Information	POC
1	Reach out to the (b) (4) sponsor and ask for the CDA and the additional data.	Stacey Adam
2	Preclinical WG to review potential ways to support acceleration of preclinical data generation for deferred agents.	Joe Menetski

Notes

- **Wave 2 Antiviral Prioritization Overview:** The team briefly discussed the approach taken for Wave 2 prioritization of antivirals and the objective: to identify compounds that agents that can be placed in a master protocol for a Phase II/III Progressive trial.
The team decided to have a 'part B' for this round of prioritization and evaluate the 12 additional compounds for which the team received surveys for (instead of deferring review for Wave 3).
- **Timeline:** Stacey also reminded the team of the timeline and that the 'part B' review materials would be sent either late evening on 7/2 or 7/3 during the day.
- **Prioritization Results:** The team went through the summary table of adjudication decisions (Below).
 - **NO-GOs:** Before diving into details, the AP group noted two entries that were pushed from deferral to 'No Gos': (b) (4). Other No-Gos included: (b) (4).
 - **Go Decision:** The team then discussed the 'go' agent selected: (b) (4). The broader Agent Prioritization group agreed that it was a good selection, and there was agreement that (b) (4) had strong data and was ready to move forward into clinical trial.
 - **Follow-up:** The team also discussed the first runner up: (b) (4). The team expressed the support for the target rationale, however, the reviewers still want access to the data before finalizing the decision.
 - **Action Item:** Stacey will reach out to the sponsor and ask for the CDA and additional data.
 - **Deferred:** The team briefly discussed that the other compounds were deferred as there was a need for additional preclinical data (e.g. (b) (4)).
 - **Action Item:** Preclinical WG to review potential ways to support acceleration of preclinical data generation for these compounds.

**ACTIV, Therapeutics-Clinical Agent Prioritization Subgroup,
Wave 2 Preclinical/Clinical Antivirals Prioritization, Meeting Minutes**

Thursday, July 2nd, 2020

Therapeutic Name	Mechanism of Action	Total Score (out of 20)	No-Gos	Decision	Rationale
(b) (4)		16	0	(b) (4)	(b) (4)
		14.8	0		
		12	1		
		9	0		
		8.2	1		
		3.3	5		
		10	2		
		9.3	5		
		7.3	3		
		5.2	2		
		5	7		

Next Steps:

- The Antiviral Subteam will begin another round of review starting after this meeting.
- The Therapeutics-Clinical Immune Modulator Subteam will also be working to organize another round of review of compounds in their area next week.

Tuesday, July 14th, 2020

Action Items

Action Items		
	Information	POC
1	Develop a proposal for optimal interim shipment of samples for analysis while trial is ongoing	Daniel Peterson / Aileen Ilaria
2	(b) (4)	Sharon Raim
3	Schedule meeting to discuss site selection	Stacey Adam

Notes

FDA Comments

- FDA weighed in on the safety monitoring approach:
 - Recommendation (b) (5)
Proposed response: (b) (5)
 - Strong recommendation (b) (5)
response (b) (5)
 - Recommendation (b) (5)
Proposed response: (b) (5)
 - (b) (5)
- What level of monitoring is expected?
(b) (5)
- (b) (4) agrees with these responses and we can reach an accommodation on (b) (4), these comments will be submitted along with the updated master protocol for the new IDN application.

Update from (b) (4) on Drug Supply Plan and Timetable

- Team is working on finalizing the CTA, trying to mirror as much as possible with ACTIV-2
- Team would like more line of sight on vanguard sites, any perceived overused US sights, etc. from a supply planning perspective (b) (4) would like some more information about how many sites will be opened initially and how many of those use a study site pharmacy vs a single site pharmacy to

Tuesday, July 14th, 2020

make decisions about drug overage. But If the number of dosages we have previously talked about are still on, we should be fine initially

- (b) (4) would be limiting for some sites. Individual site pharmacies would be necessary, which implies overage. Not expected to be a large percentage of sites and should be no issue if the initially estimated quantity of drug is available next week or the following week.
- Access to study data
 - Language around delivery of data when the trial is done (at Stage 1 if it doesn't graduate and at end of Stage 2 if it does). Language of that is in the CTA.
 - (b) (4) and NIAID are working on language harmonization in CTA for ACTIV-2 and ACTIV-3.
 - ACTION: Weekly (b) (4) specific calls with a smaller number of people will be initiated
- (b) (4) would like interim shipment of samples to generate (b) (4) while trial is ongoing. Having all samples shipped at the end of the trial would put a delay on registration filing.
 - Should have a conversation with (b) (4) to put together a proposal for what would be optimal. (b) (4) will find out whether this needs to be in the CTA. If so, this is URGENT!

Central IRB

- One impediment was NIH was requiring
- AS soon study document is finalized, Sharon can submit it to (b) (4) for central IRB submissions. Documents needed:
 - Master Protocol Document
 - Consent Form
 - Drug Information (b) (4)
 - Subject-facing Materials / Recruitment Information
 - IND
- Need to add research injury language related to COVID protocols – only apply to US sites
- FDA documentation can occur in parallel, need the safe-to-proceed letter to start any enrollment and study activities. Amendment for sponsor-level submission needs to be made before sites submit applications (b) (4) – expect quick turnaround time.
 - FDA often verbally notifies that IND is safe to proceed. Would an email or a documented phone call from there suffice? Yes.
- (b) (4) can provide approval for the pre-review. FDA comments can be submitted as an amendment.
- Jens and Jim would be the point of contact if (b) (4) varra requires clarification on any documents submitted.

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- *Do we need an attachment that covers the eConsent procedure? Or is that done at the site-level registration? That would need to be addressed at the site level.*

Site Registration

- SDMC will circulate instructions and template documents to ICCs/networks for provision to sites
- ICCs/networks to notify SDMC which of their staff need REDCap access to submit registration documents
- Vanguard sites can begin completing / collating documents and sending to ICC/network for review
- REDCap project set to go live by the end of this week
- ICCs/networks can begin entering sites' registration information as they receive / review it
- ICCs/networks can begin entering sites' registration information as they receive and review
- ICCs/networks to work with sites to set up reliance agreements with Advarra as needed

Site Selection

- CTSN and Petal are eager to start and will send a short-list of eager Vanguard sites to Jens and Jim

Chatbox - NA

Tuesday, July 7th, 2020

Action Items

Action Items		
	Information	POC
1	Discuss with the website design team whether the governance document can be housed on the website	Jim Neaton
2	Confirm whether Remdesivir can be distributed to the Wales depot to supply sites in Europe	Libby Higgs

Notes

Administration

- Funding
 - Received authorization to proceed last Thursday with payments. Funding will come in October, following SOW and RFP (scheduled for august)
 - START grant is ready to be awarded. Additional discussion on whether to utilize the grant is ongoing - advantage is the grant would last for a longer time and funding is available now
- Next steps
 - Subcontracts with distribution company to go out today
 - Waiting for insurance certificates for EU countries

Site Plan

- Site overlap discussion with ICCs and networks accomplished – alignment ~300 across networks achieved. Team is populating websites with sites' basic information at the moment. Site numbers will be assigned. This serves as the database for requesting site registration.
- Team had preliminary discussions with ICC and sites to discuss plans for site study pharmacies function.
- Initial call planned for tomorrow to determine general process for site registration and initiation

Statistics

- Statisticians on INSIGHT and DSMB worked on refining the language for the analytic plan around the interim analysis of the primary endpoint.
- Team updated the randomization plan.
- A call has been planned with Max Parmar to discuss potential implementation issues in his past experience running cancer trials.

Data Collection and Website

- Multiple drafts of the CRFs have been reviewed with most of the discussion surrounding intermediate ordinal outcome and primary outcome

Tuesday, July 7th, 2020

- Revised the safety data collection plan over the weekend. More work needs to be done in collaboration with (b) (4)
- Website has been populated with sites likely to participate, following the same INSIGHT ICC / SCC structure
- Laura McNay: Is this website a place where we can house the governance document?
 - Jim Neaton: Website includes protocol and data collection elements, open reports from DSMB and minutes from DSMB, etc. Let's discuss with the website design team.

Drug Distribution

- Worked with (b) (4) to finalize drug label
- Waiting for (b) (4) to provide draft plan for providing drug – (b) (4) will provide for the initial supply for (b) (4)
 - Working assumption is 40 sites for Stage 1 and ultimately 100 for Phase III
 - Jens Lundgren: Another aspect to consider how quickly new agents enter into the study – would need to rethink the plan in that scenario
 - Stacey Adam shared the updated estimated timeline of new agents coming into ACTIV-2 and ACTIV-3:
 - (b) (4) have been reviewed – all are in the process of requesting more data, which will inform whether agents will enter into (b) (4)
 - Team is reviewing each company's plan for Phase I trials and safety and making recommendation based on the assumption that planned Phase I readout is positive
 - (b) (4) - September; (b) (4) - end of August; (b) (4) may be for August – not yet supplied data; (b) (4) – may not be taken into Phase I (if FDA accepts studies in healthy volunteers outside of US, they can conduct Phase I on their own), late September / October for Phase III
 - Stacey shared FDA guidance on Phase I in Healthy vs. Sick Population
 - Accepts tox and safety in healthy population
 - If safety and tox study is done in healthy volunteers, some dose-ranging information (i.e., a Phase 1b) would be needed in sick patients for virology and clinical endpoints, especially in the outpatient population
- Have received (b) (4) pharmacy instructions and IB
- Next step is to develop pharmacy plan for the sites (e.g., preparing study infusion, working with clinical sites to implement randomization, etc.)
- Libby Higgs: We do have confirmation from (b) (4) (mid-July time frame)

Other Operational Issues

ACTIV, Therapeutics-Clinical Master Protocol Subgroup,
ACTIV-3 Operations Team Meeting, Meeting Minutes

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- Progress made on the procedure manual. Once CRF is done, the group will work with ICCs on the full set of procedure manual
- Data Entry Screens will be ready within a week after CRF is finalized

Chatbox - NA

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) received status updates on the ACTIV-2 and ACTIV-3 trials and discussed other topics elevated for its consideration, including joint updates from the ACTIV-2/-3 teams on vaccination post-mAb studies and a virology surrogate endpoint.

Trial Accrual and Status Updates

ACTIV-2

ACTIV-2 has activated 107 sites, including 71 sites on Version 2 of the protocol, (b) (4) on the Brii Bio arm. The (b) (4) on Version 3 of the protocol, with (b) (4) to the Camostat arm and (b) (4) to the Synairgen arm. The ACTIV-2 team is meeting with SAb today regarding chemistry, manufacturing, and control (CMC) data needed to submit Version 4 of the protocol to FDA.

The ACTIV-2 team met with FDA on February 11 to discuss a proposed change to a symptom-based endpoint for non-infused agents in the ACTIV-2 phase III trial. FDA will not accept a symptom endpoint for Emergency Use Authorization (EUA) but will consider a symptom endpoint for full applications (e.g., Biologics License Application [BLA] or New Drug Application [NDA]). Dr. Davey Smith noted FDA's decision has implications for ACTIV-2 because most of the partner companies will be seeking EUAs. The team is still considering a virology endpoint.

FDA Feedback on (b) (4), (b) (5)

FDA has recommended (b) (4), (b) (5)

(b) (4), (b) (5)

(b) (4), (b) (5)

(b) (4), (b) (5) We recommend (b) (4), (b) (5) it is important to understand potential safety signals during drug development. (b) (4), (b) (5), safety data are not available at the dosage under evaluation for COVID-19."

The ACTIV-2 team emphasized that the documentation (b) (4), (b) (5)

(b) (4), (b) (5) Implementing this approach would require (b) (4), (b) (5)

(b) (4), (b) (5) Moreover, if applied to ACTIV-6, FDA's recommendation (b) (4), (b) (5)

(b) (4), (b) (5). However, not addressing this recommendation (b) (4), (b) (5)

(b) (4), (b) (5) As a potential compromise, (b) (4), (b) (5)

(b) (4), (b) (5)

ACTIV-3

ACTIV-3 has activated 59 sites, including new ex-U.S. sites in Denmark and India, (b) (4) to (b) (4) agents in Version 2 of the protocol. An additional 23 sites are open on Version 3, (b) (4) to (b) (4) infused agent. Dr. (b) (6) noted that the DSMB will meet on March 1 to conduct safety and futility assessments of the (b) (4) agents.

(b) (4) agent and (b) (4) continuously infused (IV) protease inhibitor have been approved to enter ACTIV-3. The ACTIV-3 team had expected to launch (b) (4) in March, but the company may be unable to produce enough product by that time, likely delaying the first patient enrollment to late April. If (b) (4) demonstrate futility at the planned March 1 review, then only (b) (4) agent will continue to accrue patients unless ACTIV-3 can move other agents forward. Considering the delay with (b) (4), the ACTIV-3 team would like to accelerate the launch of (b) (4) protease inhibitor, if possible. Dr. (b) (6) indicated that (b) (4) is motivated, and the ACTIV-3 team noted they can rapidly file a protocol amendment.

(b) (4) *Protease Inhibitor*

Dr. (b) (6) expected to receive a data packet for the oral formulation of (b) (4) protease inhibitor next week and anticipated rapid approval of this agent for entry into ACTIV-2 based on preclinical data that are similar to the (b) (4) formulation. However, she noted availability of the oral formulation will lag the (b) (4) formulation by at least a month. Thus, ACTIV-3 will likely open sites with (b) (4) formulation as originally planned. Dr. (b) (6) also noted that although (b) (4) phase I study allowed (b) (4) as standard of care, resulting data have not yet been received. Based on discussions between (b) (4) and NIAID, Dr. Lane emphasized the importance of conducting studies in areas with emerging variants of concern (VOCs). NIAID is working with ACTIV-3 to ensure sites are activated in Latin America and the Republic of South Africa (RSA). Dr. (b) (6) reported ACTIV-2 is also pushing to open international sites for ACTIV-2.

Topics for Discussion

ACTIV-2/-3 Vaccination (b) (4), (b) (5)

The ACTIV-2/-3 trial teams are working (b) (4), (b) (5)

At the invitation of Dr. (b) (6), the ACTIV-2 team will meet with Dr. (b) (6) tomorrow to discuss access to the (b) (4), (b) (5). If Dr. (b) (6) can confirm access, then the team will move forward with (b) (4), (b) (5).

Dr. (b) (6) emphasized that (b) (4), (b) (5)

(b) (4), (b) (5) The ACTIV-2 team noted that (b) (4), (b) (5).
Moreover, (b) (4), (b) (5).
Dr. (b) (6) will apprise the TOC of the outcome of tomorrow's discussion.

Joint ACTIV-2/-3 Virology Discussion

Last week, the ACTIV-2/-3 teams met with (b) (4) to discuss (b) (4). (b) (4) has data comparing their (b) (4), and Dr. (b) (6) noted that preliminary analysis of data from ACTIV-3 comparing (b) (4) indicate that (b) (4).
He also emphasized that discharge from the hospital does not capture the full extent of the morbidity and mortality of COVID-19, noting that 14 percent of the discharged cohort died or had to be readmitted for COVID-19. Both study teams agree that the virology endpoint will be a good surrogate marker to enable more rapid clinical assessment for future agents. Dr. Adam will schedule a follow-up meeting.

OTAC Protocol for Human Intravenous Immunoglobulin (hIVIG)

Dr. Lane addressed concerns about potential duplication of effort between ACTIV-2 and the hIVIG outpatient study (OTAC) being conducted by NIAID with the INSIGHT network. He explained that the hIVIG study was developed last March, but the companies supplying IVIG pressed to conduct the inpatient study (ITAC) before launching OTAC. ITAC is now fully enrolled, the final cohort has almost completed follow-up, and data are expected in April 2021. For OTAC, target enrollment is between 600 and 800, with 80 percent of that enrollment projected to be from ex-U.S. sites. The ACTIV-2 team expressed interest in collaborating with INSIGHT to leverage the network's international sites to boost international enrollment for ACTIV-2 after the OTAC study concludes.

Updates on Potential Pragmatic Trial ("ACTIV-6")

PCORnet has been selected to lead ACTIV-6 and efforts are underway to engage an NIH sponsor, with NCATS considered a potential fit based on the intent to evaluate repurposed generic drugs. If an NIH sponsor cannot be secured, PCORnet has indicated willingness for the TOC to serve in an oversight capacity for the ACTIV-6 master protocol. The first drug to be tested in the ACTIV-6 study will be ivermectin; a company has already agreed to provide the drug supply as well as placebo. Dr. Adam invited TOC members to participate in daily protocol meetings at 8:00 AM. The team is also assembling a new agent prioritization committee and developing preliminary review criteria for repurposed agents. Dr. Adam noted only ivermectin will not go through the new prioritization committee; other agents, even those previously reviewed by ACTIV, will be reviewed again to ensure they meet the needs of the intended "touchless" study design.

ACTIV Therapeutic Communication Efforts

Dr. Adam highlighted a recent NIH Director's blog post promoting ACTIV's ongoing trials and including an overview of the public-private partnership along with detailed descriptions of the working groups, the trials, and the total number of agents that have been reviewed. She encouraged TOC members to circulate this update.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Samuel Bozzette, MD, PhD, Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)

Kevin Bugin, PhD, Director of Special Programs Staff, Office of New Drugs, Food and Drug Administration (FDA)

Elizabeth Church, PhD, Deputy Director, Therapeutics Research Program, Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), NIH

Judith Currier, MD, Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)

Ann Eakin, PhD, Senior Scientific Officer, Concept Acceleration Program, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)

Emily Erbeling, MD, MPH, Director, Division of Microbiology and Infectious Diseases, NIAID, NIH

William Erhardt, MD, Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants

David C. Goff, MD, PhD, Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI), NIH

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, Global Health Science Advisor, NIAID, NIH

James P. Kiley, PhD, Director, Division of Lung Diseases, NHLBI, NIH

Peter Kim, MD, Director, Therapeutics Research Program, Division of AIDS (DAIDS), NIAID, NIH

H. Clifford Lane, MD, Deputy Director for Clinical Research and Special Projects, NIAID, NIH

Jens D. Lundgren, MD, Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT

Gilbert (Lynn) Marks, MD, Senior Adviser to BARDA, Office of the Director

Sarah Read, MD, Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)

David (Davey) Smith, MD, Professor of Medicine, U. California, San Diego

OTHER INVITED ATTENDEES

Ashley Parker, PhD, Health Science Policy Analyst, NIH

STAFF

Stacey Adam, PhD, Director, Cancer, Foundation for the NIH (FNIH)

David Wholley, MPhil, Senior Vice President of Research Partnerships, FNIH

Helen Q. Chen, Consultant, Deloitte

Evan Appell, Consultant, Deloitte

Nada Saleh, Consultant, Deloitte

Alex Sorosa, Business Analyst, Deloitte

Kelly E. Beazley, PhD, Writer, Rose Li and Associates, Inc.

Appendix B: Chat Transcript

(b) (6) to Everyone: 3:14 PM

(b) (6) but I could take this question to him, if we thought it critical. We are informally dialoguing with him on ACTIV-6.

(b) (6) to Everyone: 3:16 PM

Key word may be recommend

(b) (6) to Everyone: 3:16 PM

Vs. require?

(b) (6) to Everyone: 3:17 PM

agree (b) (6) some wiggle room

(b) (6) to Everyone: 3:19 PM

(b) (6) and (b) (6) at (b) (6) are aware

(b) (6) to Everyone: 3:21 PM

good plan

(b) (6) to Everyone: 3:32 PM

I need to sign off for other mtg

(b) (6) to Everyone: 3:32 PM

(b) (4), (b) (5)

(b) (6) to Everyone: 3:33 PM

Thanks

(b) (6) to Everyone: 3:33 PM

Thank you, Ann,!!

(b) (6) to Everyone: 3:37 PM

(b) (6) does Dr. (b) (6) appreciate that OWS asked for and is paying for these studies?

(b) (6) to Everyone: 3:38 PM

Yes, he is aware. We still provide him with regular updates. However, his focus has been heavily on other items in his first few weeks, understandably.

(b) (6) to Everyone: 3:53 PM

Was all preACTIV why it doesn't have a number.

(b) (6) to Everyone: 4:02 PM

Sorry, who is the sponsor?

(b) (6) to Everyone: 4:03 PM

(b) (4)

ACTIV, Cross-Trial Operations Meeting

Thursday, February 18th, 2021

Action Items

Action Items		
	Information	Owner(s)
1.	none	n/a

Meeting Summary

- ACTIV trials progressing steadily; ACTIV-2 facing slight delays.
- Call center/ COMBATCovid traffic appear to be on the rise.
- Most issues faced during contracting were programmatic rather than legal.
- Next Meeting will be in two weeks: 03/05

Notes

Agenda

- Opening and Welcome
- ACTIV Trial Status Updates
- HHS Portal and Call Center Update
- Pandemic Response Lessons Learned Update and Contract Lessons Learned
- Meeting Recap

ACTIV Trial Status Updates (Stacey Adam)

- ACTIV-1: 38 sites open (+5 satellite sites); (b) (4)
 - 3 Host-targeted Immune Modulators
 - (b) (4)
 - Sample size (patients per arm): 540
 - Submitted Amendment 1 to IRB on 12/03 and to FDA on 12/04
 - DSMB review on 01/07 predominantly around safety; DSMB expressed no safety concern (allowed all three arms to proceed)
 - Continuing to evaluate and select participating sites
 - Jane Atkinson: Product is in Peru; hoping to have 15-20 Latin American sites open in the next 4 weeks
- ACTIV-2: 71 sites open (107 sites eligible for registration); (b) (4)
 - Neutralizing Monoclonal Antibodies and Oral Antivirals
 - nMABs (Lilly, Bii Bio, AZ, and RU-BMS), n PABs (SAB), IFN-beta (Synairgen), and camostat mesylate (Sagent)
 - Sample size (patients per arm): 421 for IV agents; TBD for others
 - DSMB review in Feb to review data from 110 patients on Bii
 - Version 3.0 activated and enrolling; FPI on Synairgen and camostat

ACTIV, Cross-Trial Operations Meeting

Thursday, February 18th, 2021

- Version 4.0 (polyclonal from SAB) to be submitted to FDA early next week; there are some delays (two weeks behind where we wanted to be); must go to CBER rather than CDER and we cannot have parallel versions under review at two separate agencies
- Bill Erhardt:
 - The Feb DSMB review will likely not happen in February, but will more than likely take place in April (despite the fact that the (b) (4) were enrolled about two weeks ago) due to:
 - Data management issues; ability of these sites to maintain reasonable pace of entering data into the electronic data capture system
 - DSMB review includes clinical and virology data; processing for virology data is a bit slow – it is being done at the University of Washington (which is also doing virology for the (b) (4) vaccine trials and those are being prioritized over ACTIV at this time)
 - Second (b) (5) : went to FDA with proposal (b) (5) ; FDA had (b) (5) ; however, the FDA did (b) (5)
- ACTIV-3: 59 sites open; (b) (4)
 - Neutralizing Monoclonal Antibodies
 - nMABs (b) (4) DARPin (b) (4) PI (b) (4) and (b) (4)
 - Sample size (patients per arm): 500 for ACTIV-3; 310 for ACTIV-3b
 - DSMB interim analysis scheduled for 03/01; Version 3.0 is up and running (AZ cocktail)
 - ACTIV-3b/ TESICO protocol received FDA feedback on 02/08; FDA pushed back on some responses, but close to resolution
 - Intending on having ACTIV-3b launched by the end of the month
 - 2 more agents have been approved (b) (4) , but there may be some supply issue, so there may be a month delay in opening up that arm of the study
 - New IV protease inhibitor (from (b) (4) approved to enter study; kick off meeting scheduled for next Thursday
- ACTIV-4:
 - (4a) Hospitalized: enrollment stopped – futility boundary achieved for critically-ill patients; superiority boundary achieved for moderately-ill patients → a therapeutic dose of unfractionated heparin was beneficial to patients and far exceeded the benefit of either a low-dose unfractionated or low molecular weight heparin; critically ill patients (those that went on mechanical ventilation) should not be receiving those agents because it was counter indicated
 - Getting ready to publish a paper that treatment with therapeutic dose heparin in moderately ill patients actually achieves a better outcome for those patients
 - Trying to get next arm of the study up and running by the end of the month
 - (4b) Pre-hospitalized: 24 sites open; (b) (4)

ACTIV, Cross-Trial Operations Meeting

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- Contract with CVS has been signed; Illinois and Massachusetts (test pilots) working with clinics to act as sites for this study; if the pilot goes well, there are plans for expansion
 - Hoping to see jump in enrollment due to CVS advancement
 - (4c) Post-hospitalized received first drug shipment on 01/05
 - Launched on 02/09 and FPI on 02/15
 - LMWH and UFH (hospitalized) and low dose aspirin, high dose aspirin, and apixaban (pre-hospitalized)
 - Sample size (patients per arm): [4a]1000; [4b] 1750; [4c] 2660
- ACTIV-5 (Big Effect Trial): 17 sites open; (b) (4)
 - Proof of Concept study to identify promising treatments
 - Risankizumab + Lenzilumab
 - Sample size (patients per arm): 100
 - Prioritizing additional investigational agents
 - The third agent has been chosen, but not yet made public; still looking for fourth agent – suggestions welcome for this agent
- The ACTIV team believes there is a lot of evidence the outpatient setting with the monoclonal antibodies that if we can pull data from our Lilly studies that there may be enough data to show correlation between virologic and symptomatic endpoint and change practice
- Bill Erhardt: Vaccine post mAb coordination: the ACTIV-2 team has drafted a protocol to look at vaccine immune responses in patients who have received mAb
 - Moderna agreed, but there is no availability at Moderna for clinical trial labeled vaccines; exploring avenues → may reach out to (b) (4) to see if they have clinical supplies that they can provide; there may also be potential with (b) (4)
- ACTIV and Convalescent Plasma Trials Status Updates
 - ITAC
 - Study closed February 10; at time of close: 24 sites; (b) (4)
 - Sample size (patients per arm): 250
 - Readout expected in early July
 - While data cleaning occurs, there are also plans for another outpatient study: OTAC (funding allocated since June 2020)
 - Potentially working with University of Maryland, Baltimore Convention Center, and Medstar Health (utilize sites to enroll participants); 20% of participants could receive monoclonal antibodies
 - CONTAIN COVID-19 (inpatient)
 - 19 sites open; (b) (4)
 - Sample size (patients per arm): 500
 - DSMB met on 02/05 to review data from the first 800 patients → received a Continue as Planned; next DSMB will be on 02/19
 - Adding up to 6 more sites

ACTIV, Cross-Trial Operations Meeting

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- Sarah Dunsmore: they have had some very good training sessions on their investigator call to focus on the use of the WHO scores for the primary outcome measures/harmonization among sites
- PassItOnII (inpatient)
 - 24 sites open (adding up to 5 more); (b) (4)
 - Sample size (patients per arm): 500
 - DSMB met on Tuesday, 01/26 to review data from first 469 patients; received a Continue as Planned; next DSMB to review 750 patient interim analysis is March 12
 - Rationale and design manuscript submitted on 02/08
 - **NCATS and FDA continue discussion on hospitalized patient convalescent plasma meta analysis (CONTAIN COVID-19, PassItOnII, VA-CURES); to be presented to trial teams in March
 - **Road to the Plasma Summit – USG debrief on Vitilant data on February 8; RECOVERY (UK convalescent plasma pragmatic clinical trial) samples to be analyzed by Broad Institute – readout expected in late February; summit planning group to meet Feb 19.
- C3PO (outpatient)
 - 52 sites released to enroll; (b) (4)
 - Sample size (patients per arm): 450 → 900 total
 - Working with 65 sites to get them open
 - DSMB met on Tuesday, 01/19 to review first interim analysis for efficacy and futility on 300 patients → recommendation to continue; next DSMB meeting is planned for 02/25 for 2nd interim analysis on 450 patients

HHS Portal and Call Center Update

(Chris Shreeve, HHS)

- Web Portal
 - Weekly Metrics Summary → beat the record every week; week of 02/08: 161, 243 visitors to the website
 - Web referrals are coming primarily from NLM sites also from unitedinresearch.com (*does anyone know that this site is?*)
 - Lilly has done their own monoclonal antibody social media campaign – the mAbs continue to be the most frequently view pages (134K page views; 71.3% of total)
 - Facebook accounted for 51% of all referrals to the site, driven by Lilly's mAb promotions
 - Google ads contributed 21.5% of traffic last week
 - Traffic to Spanish site increased tremendously driven by referrals from MedlinePlus.gov and salud.nih.gov
 - Rachel Maddox show mentioned combatcovid.hhs.gov → immediately following the segment, there were an additional 25,000 hits
- Call Center
 - Most of the calls are coming through the general line
 - ACTIV-2 is still getting most of the calls

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- Studies that have a weblink attached, people will visit the site to obtain more information
- **Please don't hesitate to reach out if you have materials that you want developed.

Pandemic Response Lessons Learned Update (Kevin Bugin, USG Pandemic Response)

- Emerging themes that were captured are highlighted in meeting deck; feedback welcome
- Discussion deferred till next meeting

Contracting (b) (4), (b) (5)

(b) (4), (b) (5)



CHAT

(b) (6) 41:24

(b) (4)

Stacey Adam 41:46

ACTIV, Cross-Trial Operations Meeting

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Thanks, Kevin, helpful!

Lili Portilla47:39

Is it possible to be more specific about the concerns?

(b) (6) 55:28

A question from me: are there commonly asked questions that the program staff would typically field? And, of those questions, are there good reasons why the answers would be expected to differ across the trials?

(b) (6) 55:33

Stacey just asked my question!

Stacey Adam56:08

Thanks, Kevin,

Stacey Adam56:16

Sorry to steal your thunder.

Deydre Teyhen58:21

Any legislative/policy relief that would have been helpful?

Lili Portilla01:01:29

For ACTIV1 I was surprised that when all was said and done the companies were cooperative

Lynn Marks01:06:28

(b) (4)

ACTIV, Therapeutics-Clinical Master Protocol Subgroup,
ACTIV-3 Operations Team, Key Takeaways

Tuesday, June 23rd, 2020

Action Items

Action Items		
	Information	POC
1	Reach out to Judy Currier (and cc Taylor Thompson) to align on the process for ACTG inpatient sites to participate in ACTIV-3 master protocol	Libby Higgs
2	Share the side-by-side endpoint comparison across ACTIV trials with Jim Neaton	Stacey Adam
3	Set up recurring ACTIV-3 Operations Team Meeting on Tuesdays from 11am to 12pm (ET)	Stacey Adam

Notes

Administration

- Funding
 - Team was notified that the supplement we submitted for the START grant will be approved.
 - This would enable some sub-contracting (e.g., drug distribution, kit prep, and ICCs).
 - Call with (b) (4) this morning; team is preparing an SOW and RFP for additional funding next week.
 - The funding we'll receive from START grant supplement will carry us through middle / end of August.
- Next Steps
 - Sub-contract
 - PETAL and CTSN will receive funding from NHLBI.
 - Team is meeting later this week with ICCs and networks on funding and site payment algorithm – would like to keep that the same across the networks.
- Laura McNay: (b) (4) would be able to send a portion of the subcontract before September.
 - Jim Neaton: Team is having conversation with them to have the full amount by first week of September.
 - Laura McNay: I'm a little nervous about that because timeline tends to slip.

Network Site overlap

- CTSN and ACTG sites would defer to PETAL when there's overlap.
- Washington ICC (overseeing US sites) and Taylor Thompson would have a conversation on overlap between INSIGHTS and PETAL.
- Team is on track to align to one funding stream.

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- Taylor Thompson: We don't want to set up two contracts for the hospital from two networks – that that needs to be mapped out. ACTG will go all in for ACTIV-2 and would defer to PETAL, same for CTSN. It is also on the table to leave the decision to the sites.
- Ginny Kan: Fully agree.
- Marissa Miller (NHLBI): How is ACTT network going to interface with these mAb trials? Are they overseeing those sites?
 - Jim Neaton: At this point, they are planning to do ACTT-3. INSIGHT has been participating in ACTT-1 and 2 but not ACTT-3. One of the investigators reach out to me last weekend. In that situation, I link them up with the ICC in Sydney. For future inquiries, I would reach out to the three networks largely in US apart from INSIGHT.
- Libby Higgs: With ACTG, we thought about using their inpatient sites when there's a wish. There's been some ambiguity with their involvement. Team is working on drafting the CTA – we would need a conversation with Judy and Peter.
 - Jim Neaton: When I last heard from Judy about 10 days ago, her position is they would defer to the other networks in participation. They would participate but through PETAL.
 - Taylor Thompson: Some sites have terrific inpatient ACTG presence. We will have a conversation with ACTG and define a process for participation.
 - Libby Higgs: I'll reach out to Judy and cc Taylor. I would think they have sites who want to participate that are not PETAL sites.

Statistics

- Initial DSMB review of protocol next week – been having conversations with statisticians on blinded an unblinded roles
- Started a group to discuss data analysis plan
- Also started a group to work on randomization app for trial design. Once developed, it would be circulated to the statisticians involved in this program and then to all investigators on this team

Data Collection, Website, and Drug Distribution

- A group started drafting case report forms. There will be a call later today to talk about experience in PETAL to collect sustained endpoints with data collection CROs
 - Team will try to align with what is done in the hIVIG study as some sites are doing both protocols.
- Website
 - Updated the INSIGHT website to include ACTIV-3
 - Team uses the website extensively for reporting
- Drug distribution
 - Working with PCI and calls scheduled with Lilly next week
- Yves Rosenberg: To what extent is data collection standardized with ACTIV-2?

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- Jim Neaton: There is not a lot of standardization with ACTIV-2. They are an outpatient trial - by design data collection would be different. Maybe there could be some standardization on safety outcomes.
- Stacey Adam: If helpful, we can share a side-by-side endpoint comparison across ACTIV trials.
- Jim Neaton: That would be helpful. I was going to connect Michael Hughes on their data collection forms design. There is some overlap across studies, so it is important to standardize.

Areas for Help

- Some issues that we may need help from CRO – (b) (4) has capabilities to possibly serve some of these functions for us – more discussion in coming days
- Still outstanding
 - Agent information into EV's extended medical product dictionary
 - Peer-to-peer / gateway reporting
 - Assistance with EU sponsorship functions (CHIP)
 - Call scheduling / notes
 - Monitoring in some countries (support through ICCs)
 - CSR reporting (if not possible by pharma)

Discussion

- Marissa Miller: Can you expand on co-enrollment in this trial if patient starts to compete?
 - Jens Lundgren: Protocol states that patients are committed to this trial for the first 5 days. If the need to roll off, there's a possibility after Day 5.
- Jens Lundgren: We have been discussing with hVIG trial to build the concept of local pharmacy to support several sites. That would require two things: 1, close proximity for logistics (infusion needs to start within 4 hours after bag is prepared); 2, agreement to receive drug from another institution. The advantage of this model is it would require fewer locations. We need to explore that possibility. Team is currently drafting a document to further spell out the requirements and can share with the group.
 - Ginny Kan: We had similar plan with one of our ICCs
 - Taylor Thompson: In certain states, we had some regulatory issues involving research pharmacies moving investigational product from hospital to hospital. These drugs would also require temperature control and monitoring during transportation – which makes it a little complicated.
 - Jens Lundgren: Of course, we need to be observant of local regulation and policy.
 - Jim Neaton: This is a big operational issue in my mind. We will likely get several lots of drugs. It would be hard to move them once they are distributed to sites.

**ACTIV, Therapeutics-Clinical Master Protocol Subgroup,
ACTIV-3 Operations Team, Key Takeaways**

Tuesday, June 23rd, 2020

- Taylor Thompson: I agree. The hub-and-spoke distribution model would be feasible. We can ask local pharmacy to serve this role.
- Team agreed to have recurring calls at this time to discuss operational issues. Stacey is also setting up recurring joint ACTIV-2 and ACTIV-3 Stats Meeting.
- Yves Rosenberg: Is there an update on the timeline?
 - Jim Neaton: Lilly is still doing Phase I, we are waiting for FDA comments and have to go back to FDA with the Lilly appendix. My guess is end of July.
 - Team does not foresee any major issue with database build.
- Aileen Ilaria: Do we know when we'll be seeing a CTA? Would use what we agreed with ACTIV-2 as a starting point?
 - Libby Higgs: We took the draft CTA DAIDS has done with Lilly and used that as template. Team is close to send a draft that is representative of the mutual understanding.
- Jens Lundgren: What's the potential timeline for Investigational Agent #2?
 - Stacey Adam: We had our first meeting Agent Selection Committee (ASC) meeting last Saturday and went through logistics and process. The group has agreed to push through 2-3 agents this week. Materials will be distributed tomorrow for review. The Trial Oversight Committee will have the first meeting on Thursday / Friday. Team will meet again next week to review ASC's recommendation. Team should see something towards the end of next week / beginning of the following week.

Chatbox

From Libby Higgs to Everyone: 11:03 AM

Yes cause and effect!

From JLUN0029 to Everyone: 11:21 AM

yes, I will be on that call Jim

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Action Items

Action Items		
	Information	POC
1	Share the Operations Updates slides presented during the meeting with the team	Jens Lundgren / Stacey Adam
2	Follow up with Gregg Larson after checking with NIAID on agreement with (b) (4)	John Tierney
3	Coordinate an offline conversation on subcontracting for site monitoring support	Susan Vogel
4	Share information on the no-touch REDCap consent technology with Jens Lundgren	Taylor Thompson
5	Include Rachel Harrigan in site selection conversations	Jens Lundgren

Notes

Administration

- Team received some information regarding funding – application for supplement to the grant would go forward. Award would arrive next week.
- (b) (4) received authorization to proceed with funding expected on July 6.
- Team has two funding sources, both ready to go next week. Once we have certainty which would be ready first, we'll go with that.
- Next steps:
 - Move forward (b) (4) comes through
 - Copenhagen ICC has obtained CT number to put on drug label
 - Moving forward with insurance certificates for EU
 - ICC funding algorithm was reviewed last week and over the weekend - all collaborating networks seem comfortable with the proposed payment structure.

Network Site Overlap

- CTSN and ACTG defer to PETAL where overlaps occur
- Allocation of overlaps between INSIGHT and PETAL have been resolved.
 - Annetine Gelijns: Had a great discussion about overlapping sites, only PETAL site that remains in CTSN would be Duke and Sinai on the INSIGHT side
- Discussion about non-overlapping sites with ACTG is ongoing

Site registration

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- REDCap project database will be used to collect information and documentation about sites.
- The ICCs or networks will be responsible for entering or uploading this information for their sites.
- There is an initial registration instrument, an information update instrument, and a deregistration instrument.
- Information on necessary documents will be distributed on July 6. REDCap project will be available the week of July 15.
 - Taylor Thompson: Team has phoned all PIs involved on the realignment and received support - good collaborative spirit

Statistics

- Assignment made for the first stage between blinded and unblinded statisticians
- Data analysis plan will be revised based on the DSMB reviews
 - (b) (6) : There are some discussion (b) (5) . Team expects written comments by Thursday.
- An internal group has been established on how to handle randomization at the SDMC. That group will report to this team for final review.

Data Collection and Website

- Committee established with representatives from the SDMB, ICCs and collaborating networks to review CRFs. Team expects multiple revisions.
 - (b) (6) Subgroup is meeting just after this call to discuss (b) (5)
[REDACTED]
[REDACTED]
[REDACTED]
- Team made internal structure changes for the website to incorporate additional networks. Team has agreed on design parameters. Website construction is underway.

Drug Distribution

- Draft for drug label is under review
- (b) (4) desired to establish process for drug request. The initial request for Stage 1 would be small. Request for Stage 2 and would require a 3-week lead time.
 - Jens Lundgren: Team had a discussion with (b) (4) on Sunday and the company confirmed that they will provide sufficient amount to complete Stage 1.
 - Aileen Ilaria: Correct – the initial shipment would be sufficient to complete Stage 1. Team also needs to understand the geographic distribution of the sites to use hubs to optimize distribution.
 - Gregg Larson: (b) (4) has two central hubs – (b) (4) Drugs will be sent there and from there shipped directly to the site pharmacies. In some cases, (b) (4) uses

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currier depots in (b) (4) The initial distribution would be limited to those two locations.

- Rachel Harrigan: Is remdesivir being distributed in the same fashion?
 - Jens Lundgren: Yes.
 - Rachel Harrigan: (b) (4) has received multiple contacts from ACTIV teams. There will be a central OWS contact with (b) (4).
- Gregg Larson: I've received an inquiry about any agreement in place (b) (4)
(b) (4)
 - John Tierney: I will follow up with stakeholders at NIAID later today and let you know. (b) (4) will provide letter of cross reference for all ACTIV studies.

Other Operational issues

- Team has developed outlines for ACTIV-3 procedure manual and training materials with collaboration with ICCs and participating networks.
- Team is testing query systems and started to build data entry screens in parallel with the development of the CRF.

Areas for help

- Agent information into EV's extended medical product dictionary
- Peer-to-peer / gateway reporting
- Call scheduling / notes
- Help with monitoring in some countries and Washington ICCs
 - An offline discussion around subcontracting for site monitoring to be coordinated by Susan Vogel.
- (b) (6): We've recently developed a (b) (5) - happy to share that with the team. PETAL network is strongly inclined to have a (b) (5).
 - (b) (6): We have checked with the single IRB – they do not have a specific requirement for (b) (5) the protocol but it would need to be specified in the protocol (b) (6) will be used. It would be difficult to develop (b) (5) centrally, considering the different regulatory requirements it would need to meet, and trying to maintain multiple versions (b) (5). Team has aligned on leaving that implementation to the sites. It would be quicker for them to use their standard procedure.
 - (b) (6): That's good news on the central IRB ruling. Team has made a good choice considering (b) (5), various versions etc (b) (5) is good for site monitoring – we would take this internally to see if it would work for PETAL can see if we can mock up some SOP for someone interested.

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- (b) (6) expressed interest to learn more about the (b) (5)

ACTIV-2 and 3 Strategic Documents

- The document is intended to be a central resource for everyone, and it can be housed on the ACTIV-3 portion of the INSIGHT website. The document contains project management content, including program structure, vendor list, contract relationships, project plan, governance, RACI, etc.
- This is intended to be a fluid document and team welcomes feedback
- Rachel Harrigan: It would be helpful to have a timeline for all IAs anticipated to arrive for ACTIV-3. This has interdependency with requesting commitment of resources
- Rachel Harrigan: OWS Clinical Ops also requested recruitment strategies for each study, including timeline and goals.
 - Jens Lundgren will include Rachel Harrigan in ACTIV-3 site selection conversations
- ACTIV-4 will have an inpatient trial for anticoagulants. Their DSMB review is scheduled for mid-July.
 - (b) (6) : We'll want to (b) (5)
[REDACTED]
[REDACTED]
 - Rachel Harrigan: ACTIV-4 is in still in protocol design phase but it is a large open label study (expecting 7,000 to 10,000 patients). Team is doing some epidemiology modeling work predict site selection which would assist with overlap resolution.
 - There is a call later today to demo the (b) (4) developed by the (b) (4)
 - (b) (6) : This is important (b) (4) .

Chatbox - NA

Tuesday, June 16th, 2020

Action Items

Action Items		
	Information	POC
1	Follow up with Jim Neaton / Jens Lundgren on INSIGHT international sites represented in the CTC dashboard	Elizabeth Desrosiers
2	Include Jim Neaton in the meeting with MediData on data coordination	Stacey Adam

Notes

Master Protocol Status Update

- Changed primary endpoints to “time to sustained recovery”, defined as being out of the hospital for 14 consecutive days); no change in sample size
- Clarified that drug can enter either through Stage 1 or directly to Stage 2. Phase I trial would require a separate protocol
- Activities measures for Stage 1 changed
- Inclusion and exclusion criteria updated
- Working on defining the criteria for standard of care
 - Example of how fast standard of care can evolve: statement from RECOVERY study released today
- Protocol to be sent for pre-IND tomorrow morning
 - (b) (6) : We are submitting protocol for FDA for comments. Combined with FDA feedback on (b) (5)

Operations Update

- Multiple participating network
- Meeting last Thursday with PETAL and ICCs to lay out a plan for how work to be done can be distributed. 15 tasks typically assigned to ICCs are allocated to network leads to execute. Discussed whether additional support from CRO would be needed for task execution
- Typically, each ICC works with multiple countries. The site coordinating center (SCC) takes responsibility for sites in that region.
- Two potential CROs INSIGHT has been working with can be used for ACTIV-3:
 - (b) (4)
 - (b) (4)
 - (b) (4) doesn't have a central laboratory. Expected work includes antibody testing and markers of inflammation and coagulations. Has worked with NIH labs previously and anticipate that is the approach

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- PETAL and CTSN expressed they can perform the tasks with their existing infrastructure. They planned to look at site overlap, need to sort out whether those sites would resume responsibility
- VA decided not to operate as a separate ICC but team up with INSIGHT Washington ICC to be treated as an SCC
- CRO Needs
 - None for PETAL and CTSN
 - Site monitoring – typically we develop a protocol and forms. Depending on the extensiveness, could require monitoring needs. Washington ICC/VA expressed needs, and possibly in other countries
 - Washington ICC also expressed need for procurement, distribution, and translations
- Shared functions - More details to be determined
- Other help identified – could be done either at one of the ICCs or with CROs; potentially need help

Discussion

- Laura McNay: In complete support of Jim's plan and have a good path forward
- Yves Rosenberg: Potential concern around trial monitoring
 - Jim Neaton: Agree. We've simplified the trial to streamline monitoring. We've taken a risk-based approach to monitoring – it's doable and not dissimilar to what the other networks were doing.
 - Taylor Thompson: Agree. Risk-based monitoring plan is what we do already and should be suitable to task. Will fold in the per patient cost to have someone not involved in data management to do that for us – that's manageable. PETAL is equipped to do this.
 - Laura McNay: Key is to be as simple as possible.
 - Annetine Gelijns: Don't see any issue for CSTN.
- There's alignment of thinking across the networks on many levels.
- Stacey Adam: (b) (4) between NIAID and (b) (4) would cover this one?
 - Sarah Read: (b) (4) ACTG but we are working on it at the moment.
 - Libby Higgs: Approach is to invite (b) (4) as a party and have them distribute the information to the participating networks.
- Stacey Adam: Any chance for joint (b) (4)
 - Libby Higgs: That's also in the works. The hope is we have visibility for which product will enter which study to streamline the process.
- Jim Neaton: Want to make sure that these (b) (4) Laura is aware of it and is working on it.
- Libby Higgs: Access to (b) (4) through NIAID

**ACTIV, Therapeutics-Clinical Master Protocol Subgroup,
ACTIV-3 Operations Team, Key Takeaways**

Tuesday, June 16th, 2020

- Laura McNay: We are putting together list of sites and overlay with geographic location of pandemic to inform site selection decisions.
 - CTC Working Group is also working on the dashboard to overlay sites and pandemic forecast
 - Jens Lundgren: Granularity with international sites is not fully represented on the map. Would like to put the drugs to local depots and pharmacies – should delegate a subgroup to work on getting site information to the CTC to supplement?
 - Jim Neaton: Easiest way to get this information is from the INSIGHT, PETAL, and CSTN websites. Can it be pulled from there?
- For ACTIV-2, (b) (4) is taking on data coordination and going to talk to (b) (4) on related capabilities. (b) (4) I would like to be part of that conversation.

Chatbox - NA

Monday, June 15th, 2020

Action Items

Action Items		
	Information	POC
1	Arrange a meeting between INSIGHT (including EU and UK representatives) and NIAID contracting stakeholders to discuss confidentiality agreement of Lilly compound(s) and plan for regulatory for operating at international sites	Stacey Adam

Notes

Opening

- Team has received approval for Lilly to enter the study

ACTIV-3 Update [Refer to Jens' Presentation]

- Team had a helpful CSRC review last Friday and received consolidated feedback. Team has worked over the weekend to finalize the master protocol in order to submit to FDA on Wednesday.
- Hypothesis has been tweaked -
 - Primary endpoint has been modified to "time to sustained recovery".
 - Team maintained the view that investigational agents could be modulating host immune system or directly impacting the viral pathway.
 - Standard of Care is Remdesivir plus supportive care (more in appendix E).
- In the earlier version, agent can come in in one of the three ways. Now, there are two direct pathways for entry: One, if Phase I data is available, agent will enter in Stage 1 then potentially progress to Stage 2; Two, if there is already compelling safety and preliminary efficacy data, agents can enter directly to Stage 2
 - In Stage 1, up to 3 doses are allowed. Only 1 dose is allowed to progress to Stage 2.
 - There is still the option for a Phase I study (i.e., dose escalation). It will be done in a separate protocol (described in Appendix G). This is to eliminate the confusion about the Phase I study in the protocol and focus on Phase III.
- Team received some feedback on Section 2.3, particularly around how investigational agents are identified. To that end -
 - Governance is clarified: There will be an overarching Trial Oversight Committee for ACTIV-2 and ACTIV-3, who will select agents, guided by the Agent Selection Committee. There will also be a joint DSMB across the two trials.
 - The investigational agent can be one or more than one component.
 - During the conduct of the trial, two agents may be compared to each other or combined. One agent may become part of the standard of care during the trial. Right now the trial is designed for superiority but it can also test for non-inferiority.

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- Michael Proschan: That might involve a lot of comparisons if you allow comparisons against each other.
 - Jens Lundgren: Yes. The way it's written now, every component is compared to placebo. A scenario may arise that we want to compare across agents. This is just a scenario and not the intent to compare Agent A and Agent B. One such scenario could be that the first wave of agents proves to be effective and then the second wave agents could be more effective, then it might make sense to do that comparison.
 - Michael Proschan: Generally, companies didn't like that idea when the topic came up in the past.
 - Libby Higgs: Particularly if we are looking at different doses, we will be looking at multiple comparisons.
 - Jens Lundgren: That would only be the case in Stage 1.
 - Michael Proschan: Is this only applicable for Stage 1?
 - Jens Lundgren: No, we can have all sorts of permutations. We would need to finesse the language.
- Sandeep Menon: We may need to define what success looks like for agents. I understand the concern – sponsors like to compare to the placebo. We would need some guidance for graduation, otherwise we will take too many me-too's into Stage 2 of the trial.
 - Jens Lundgren: The Trial Oversight Committee would need to weigh in.
 - Sandeep Menon: Yes. We would like to help them with some specifications here.
- Jens Lundgren: Do you see the non-inferiority situation arise at some point?
 - Michael Proschan: You'll come up with non-inferiority margin based on something, I guess?
 - Jens Lundgren: We don't want to go into details on how to design but would let it hang out there as a possibility. At the moment, it's for each agent to compare to placebo. There has been discussion on what the boundary is.
 - Sandeep Menon: We might not be powered for the non-inferiority. That might be a challenge.
 - Jim Neaton: Protocol would have to be very different for non-inferiority. Is it worthwhile to even discuss the possibility within the boundary, or should we say if that arises a new protocol would need to be developed?
 - Michael Proschan: I worry about making it too all inclusive. It's like saying "adaptive method may be used" without specifying what the methods are.
 - Jim Neaton: Point taken.

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- Primary endpoint has been modified to “Sustained recovery – being alive and having been out of hospital for 14 consecutive days”. A number of patients either die very quickly or get re-admitted to the hospital within 2 weeks after the initial discharge. Team questioned whether the initial discharge is sufficient for recovery.
 - Team has changed the thinking around what “hospital” means. Not every patient who is leaving hospital is discharged to home but rather to a recovery institution.
 - The impact is less people might “recover” using this definition, which has a potential impact on sample size.
 - Jim Neaton: I don’t think this will have an impact on sample size on the 90-day follow up period. This involves some assumptions that we don’t have data on. We have a sample size estimation, and we can adjust if we don’t think we’ll hit our target. Based on data from ACTT-1, people who enter the study in Stage 1 should all recover by this outcome. There is a question mark around people who enter in Stage 2. We are exploring the new outcome here. I don’t think it has a major impact on sample size. This is a better outcome that reflects true recovery.
 - Michael Proschan: It’s a good decision and a good compromise to use 14 days. Longer (i.e., 28 days) becomes tricky when you are monitoring, especially when you are looking at going all the way out to 90 days. I do think its more likely people could be re-hospitalized. This is a well-reasoned decision.
 - Taylor Thompson: I’m comfortable with this change. It is a “get home and stay home” endpoint. The “stay home” part is the sustained part, and home is broadly defined as residence where you acquired COVID-19 (e.g., group home, nursing home, etc.).
 - Annetine Gelijns: It is a much more robust primary endpoint. It is also more patient centric – out of hospital and sustained. I’m in total agreement.
 - Michael Proschan: To raise a technical point – if they go to their family residence for family support for the first week after discharge? Does that count? Maybe we need to refine that language.
 - Yves Rosenberg: I agree that it makes sense. It would make it more complicated in terms of operations of protocol execution and follow up.
 - Jim Neaton: The advantage of time-to-discharge is its simplicity. This would require much more effort on our part to avoid missing data.
 - Taylor Thompson: In our experience, the lost to follow-up is 1-2%. We added language in the upfront consent that allows us to call these facilities. The only variation is to get vital status 14 days after discharge. There would be very little lost to follow-up.
 - Jim Neaton: I agree. It would be harder if our initial goal is zero lost to follow-up

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- We are not going to discuss the activity endpoints now – team still needs to solidify the agreement. The group would start adding descriptive language for each item so it's clear what we mean.
- Secondary endpoints haven't changed a lot. We agreed to sample blood at baseline, Day 1, 3, 5, 28, and 90. It is fairly intense sampling to follow the initial kinetics of the antibody. Is this ok?
 - Group agrees that it is acceptable.
- Inclusion criteria has been simplified to only 4.
- We built in additional exclusion criteria for stage 1 only – Excluded patients with extrapulmonary diseases and is on mechanical ventilation at the time of entry. These patients can still enter Stage 2. Team is putting that language in the consent.
- Outstanding Issues
 - Jim Neaton: Dean Follmann mentioned at the CRSC review that he has developed a simulation to look at criteria going from Stage 1 to Stage 2 and has arrived at similar decisions. He requested to build in more rationale for Type 1 and 2 error rates for Stage one - we will have a discussion with him about that.
 - Michael Proschan: There are different ways to look at it. It is an interesting question about optimal alpha for the first stage, optimal information time, etc.
 - Section 10 stats can be done today
 - Generic Appendix H and I –
 - Appendix H describes the investigational agents. There is a template in front and H1, H2, etc. will be built out on top of that.
 - Appendix I describe the standard of care. We have received some suggestions and input from CSRC on principally what are the arguments. That may change over time. Team has developed some language around how to do that. It is also important to include some supportive care – we need to specify what we mean by that.
 - Team has confirmed from (b) (4) that their compound will enter this protocol. Team has met with (b) (4) yesterday and will develop (b) (4)

Next Steps

- Stacey Adam: I will continue to let you know all agents that we are assessing. Currently there are 4 other agents. All would need to be vetted and approved by the Trial Oversight Committee. I will let you know the timelines for these agents.
- Jens Lundgren: Principle issue is around sharing information, materials, and data as we get these agents to come in. Confidentiality agreement, access, level of details, etc., is that something the Trial Oversight Committee has considered?
 - Judy Carrier: Companies have disclosure agreement that covers the investigators on the trial. That's how ACTIV-2 has set it up.

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- Stacey Adam: Either the CDA in place for ACTIV-2 also covers for ACTIV-3, or anyone who's not covered under that CDA will have a confidentiality agreement. I assume it would be covered by the NIAID one (either through existing or through an amendment). Once approved, it will be handed over to NIAID for negotiation and contracting.
- Jim Neaton: If we are going to take over sponsorship in UK and EU, there's information from the IND file that we typically won't need - only sponsor NIAID would need for FDA - but we would need for authorities in Europe. This issue has arisen previously. It's a bit broader set of information one would need to do this internationally as to what's needed for these agreements, referencing the NIAID file.
 - Stacey Adam: Let's have a conversation with some of the NIAID contract folks to talk about what the process would be and how quickly we need to get that going with our plan to activate international sites.
 - Jim Neaton: That would be a good starting point. We should involve some people from EU and UK (e.g., Jens Lundgren) who can speak to their regulatory requirements.
- Jens Lundgren: For (b) (4) when will we get more details on (b) (4)?
 - Stacey Adam: Jonathan Green would be the person to contact to find out about whether ACTIV-2 CDA covers ACTIV-3
 - Sarah Read: I have just sent a note to Jonathan and Peter copying Libby.
 - Jens Lundgren: Once we have documentation in place, we will discuss separately (b) (4).
- Submission to the FDA would go through JT.
 - Libby Higgs confirms.

Chatbox

N/A

High-Level Meeting Summary

The TX-Clinical Monoclonal Antibody (mAb) Steering Committee (SC) convened to review results from the neutralizing antibodies clinical summit, next steps for trial governance and agent selection, and updates on ACTIV-2 and -3 master protocols.

Neutralizing mAb Clinical Summit Recap

The summit generated interest in submitting neutralizing monoclonal antibodies (mAbs) to the ACTIV network from companies such as AstraZeneca, (b) (4) GSK, Lilly, and VIR. Drug companies will be sent an FAQ document to answer questions posed at the summit. The deadline for compound submissions is June 13. Funding has also been provided to NIAID for sites involved in ACTIV.

Next Steps for Trial Governance and Agent Selection

Dr. Stacey Adam reviewed the governance hierarchy for ACTIV-2 and -3, which consists of an Agent Selection Committee (ASC), Trial Oversight Committee (TOC), and ACTIV-2 and -3 Protocol Leadership teams, with NIAID as the trial sponsor. The structure has been designed to balance the desire for speed with the need to ensure public trust in the drug development process; well defined roles must be in place to avoid apparent or actual conflicts of interest.

Agent Selection Committee

The ASC, which will identify mAbs (and potentially some polyclonal compounds), will not have industry representation. It will include four NIH members, four external academic experts without industry ties (13-15 are under consideration), and two members of OWS (who have already been selected); membership should be finalized by June 15, 2020 with a projected first meeting on June 17.

Trial Oversight Committee

The TOC is being established in parallel with the ASC. This committee, which will replace the mAb SC, will be composed of ACTIV, NIH, OWS, *ex-officio* industry scientists, and community advocates. ACTIV-2 and -3 network leadership and PIs will attend TOC meetings for consultation and feedback but will not have voting privileges. ACTIV, OWS, NIH, and FDA leadership will nominate their respective representatives to this committee (Dr. Janet Woodcock will serve as one of the OWS representatives) and Dr. Sarah Read will assist in identifying community advocates. The TOC is projected to be finalized and conduct its first meeting by June 19.

Dr. Adam noted that while the TOC has not been finalized for ACTIV-3 testing, it will approve Lilly's mAbs because they have already met the arguably more stringent criteria of ACTIV-2 clinical testing. However, official OWS approval may be required.

Drs. Woodcock and Jens Lundgren suggested that the TOC may need to communicate with external government-funded research groups and private research groups to minimize redundancy of mAb testing for similar indications and target populations. Any compound

submitted to ACTIV should not also be tested by the submitter in parallel to maximize efficiency; FDA typically requires multiple efficacy trials, but not in a crisis.

Protocol Leadership Teams

The ACTIV-2 and -3 protocol leadership teams are already established and have been regularly meeting. However, industry representatives will be integrated into these meetings as new companies are selected for compound testing. Dr. Judith Currier advocated for establishing an ACTIV-2 subgroup to address compound-specific matters, in addition to holding periodic meetings with all company representatives to address issues that affect all compound developers.

An ACTG representative may need to join the ACTIV-3 protocol leadership team (especially if ACTG sites will be needed for ACTIV-3 studies) and an INSIGHT representative may need to join the ACTIV-2 team to allow for cross communication between the two teams. ACTIV-2 and -3 network sites may also need to be surveyed to coordinate their use by both protocol groups; the ACTIV TX-Clinical Capacity WG has already begun to inventory all available ACTIV-3 network sites to further this goal.

Both protocol leadership teams may need to provide additional guidance (e.g., detail specific process and endpoint expectations) for small companies that wish to investigate dosage findings and conduct early phase clinical trials of promising compounds but have less clinical trial expertise than large manufacturers.

ACTIV-2 Master Protocol Update

FDA is reviewing the ACTIV-2 master protocol. The ACTIV-2 protocol team has established its budget and logistics to rapidly initiate testing within its network sites as soon as the protocol is approved. Small molecules (e.g., antivirals and immunomodulators) may also be included as an amendment to the master protocol but will require the approval of OWS and may need to cede priority to mAbs. ACTIV will also need to increase community participation in clinical studies using communication networks developed by entities such as RADx and All of Us.

ACTIV-2 is projected to begin on July 6 using compounds from Lilly. Drs. Lisa LaVange and Karen Price noted that, as multiple trials commence, Bayesian statistical analyses may be employed to use data from one study to inform and potentially speed the progress of another. For rigorous cross-comparisons of compound treatment effects both within and across clinical phases and ACTIV protocols, similar testing endpoints must be obtained. ACTIV-3 may also join ACTIV-2 in cross-study statistical comparisons of treatment effects.

ACTIV-3 Master Protocol Update being discussed

Dr. Lundgren reviewed the primary and secondary recovery outcomes for inclusion in the ACTIV-3 master protocol for inpatient compound testing. The primary outcome is defined as the time to hospital discharge, or removal from supplemental oxygen or ongoing medical care (e.g., situations when hospitalization is extended to control infection rates or to secure living accommodations outside the hospital). Secondary outcomes include time to recover and

mortality 90 days after hospital discharge. An additional secondary outcome that the team may include is time to sustained recovery, defined as patients remaining out of the hospital for 28 days after discharge. The protocol team does not plan to limit the proportion of patients with organ failure in the studies, but they estimate that 40% of patients studied will be severely ill.

Based on feedback from the NIAID DAIDS Clinical Science Review Committee (CSRC), the protocol team will modify the standard of care (SOC) section of the protocol, which currently states that patients will receive remdesivir unless contraindicated. The CSRC noted that remdesivir is still an experimental drug, which may not ultimately prove to be SOC in all countries; moreover, its inclusion in the protocol, combined with potential weaknesses in the supply chain *outside* the protocol, may raise ethical concerns. However, the team plans to work with the CSRC to retain remdesivir as SOC in practice until a new standard emerges. The team will also develop the rationale for its statistical endpoints and may harmonize endpoints with those in the ACTIV-1 protocol. The modified protocol is expected to be completed by June 16; it may then be submitted for FDA pre-IND approval simultaneously with further review by the CSRC.

Next Steps

This meeting is the committee's last. Members may contact Dr. Adam if they have ideas for other uses of this committee or would like to be considered for TOC membership.

Appendix A: Participants List

MEMBERS – STEERING COMMITTEE

Samuel A. Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), NIH*

Joan Butters, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT*

Gilbert “Lynn” Marks, MD, *Senior Adviser to BARDA, Office of the Director*

James D. Neaton, PhD, *Professor of Biostatistics, University of Minnesota and Principal Investigator, INSIGHT*

Karen Price, PhD, *Senior Research Advisor, Statistical Innovation Center Lead, Eli Lilly and Company*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Janet Woodcock, MD, *Therapeutics Lead, Operation Warp Speed*

INVITED PARTICIPANTS

Kevin Bugin, MS, RAC, *Director for Special Programs, CDER, FDA*

John Farley, MD, MPH, *Director of Office of Infectious Diseases, CDER, FDA*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Karen Tountas, PhD, *Scientific Program Manager, FNIH*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

Dave Frankowski, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From (b) (6) **to Everyone: 01:31 PM**

Jim and Jens: what will you do if Remdesivir supplies are interrupted?

From (b) (6) **to Everyone: 01:47 PM**

I believe that NIAID has some 400,000 contacts who wrote in with interest of getting serology and is planning to do antibody testing on 10,000. Might be another source of patients.

Tuesday, June 9th, 2020

Action Items

Action Items		
	Information	POC
1	Meet to discuss and align on network capabilities and additional operational needs required to implement ACTIV-3	Jim Neaton / Annetine Gelijns / Taylor Thompson / Vicky Davey

Notes

Opening

- ACTIV-3 master protocol went to CSRC review last night.

mAb Clinical Summit Update

- Stacey Adam shared the agenda of the mAb Clinical Summit
 - Co-led by ACTIV and Operation Warp Speed
 - Governance
 - Regulatory Perspective
 - Gating Criteria for mAb – will also discuss whether to allow combinatorial treatments
 - Master Protocol Design
 - Clinical Operations & Get Company Feedback
- Hope is for verbal commitments from companies
 - Know (b) (4) is committed but would like more
 - From landscape analysis: 45 companies with mAb – 12 of them may have good candidates by end of the year. Still hoping for 4-5 of companies to give verbal commitment for participation after the summit

ACTIV-3 Protocol Update [Refer to Jens' Presentation]

- Changed the hypothesis slightly – keeping it more generic (e.g., specifying Remdesivir as standard of care in the appendix to allow changes); no change in primary endpoint
- Two ordinal outcomes: pulmonary+ (which includes extrapulmonary manifestations) and pulmonary. For graduation to Stage 2, proceed if there is activity in both scales, cease if there is no activity in either scale, or DSMB will review to make a decision if there is non-concordance
- Yves Rosenberg: Do we plan to look at morality or time to recover at Day 28 as secondary outcome?
 - What's shown on the slide is top line; the protocol contains a detailed list of secondary outcomes.

Operations Discussion

Tuesday, June 9th, 2020

- NIAID is trying to harmonize as much as possible between ACTIV-2 and ACTIV-3
 - One central IRB to be shared between ACTIV-2 and ACTIV-3
 - One DSMB that oversees both studies to facilitate crosstalk between the studies
 - Laura McNay will send something on structure shortly
- Been having in-the-weeds discussions regarding operations. No final decision yet. Would surface to the leadership for final decisions – looking to Jim Neaton on timing of that
- Jim Neaton: It's been nonstop protocol writing with two other networks. Has not talked about operation issues. Planning to connect with Annetine Gelijns, Taylor Thompson, and Vicky Davey to discuss
 - INSIGHT has been successful with this type of trials because of its international presence
 - Responsibility as a sponsor is shared with international coordinating centers (ICCs)
 - In collaboration with the partnering networks, propose to view the partnering networks as one ICC. They have a set of sites and will assume responsibility to help manage conduct at those sites (e.g., protocol registration materials, transmission of safety data to UMN, translations needed for ex-US sites, following up on queries, etc.)
 - INSIGHT has long-term working relationship with a central repository - established system for pulling and tracking that is integrated with data management. Would prefer using the same specimen repository located in Jersey. Don't need CRO support in that area
 - INSIGHT has been working with (b) (4) for distribution. They have capability to receive, QP, release to sites, etc., not only in US but also in Europe. Issue is we don't know what the drugs are, how they are received, storage requirement, etc. (b) (4) might work for some of it - need to better understand (b) (4) capabilities before making a decision
 - Want to have conversation with Annetine Gelijns, Taylor Thompson, and Vicky Davey to understand their capabilities and needs before agreeing to engage with (b) (4)
- Laura McNay: We should absolutely keep the existing contracts and capabilities you've used before - would use (b) (4) to support the structure you already have
 - Jim Neaton: Appreciate the offer. We need to have a broader conversation with partnering networks and INSIGHT ICCs on how best to do that. Would like to take some time to assess more carefully
 - Annetine Gelijns, Taylor Thompson, and Vicky Davey are looking forward to further discussions
 - Taylor Thompson: Should also include Wesley Self at Vanderbilt)
 - Jim Neaton: We would work with ICCs and the partnering networks to centrally design and would rely on them to implement
- Libby Higgs: We are just getting ourselves organized. We are looking to INSIGHT to lead and happy to support where needed

ACTIV, Therapeutics-Clinical Master Protocol Subgroup,
ACTIV-3 Operations Team, Key Takeaways

Tuesday, June 9th, 2020

- Stacey Adam: What support do you need from ACTIV (e.g., facilitate meetings)? Do you need CTC WG support / collaboration?
 - Jim Neaton: I would defer answering that question till after we discuss with the partnering networks. Can keep this meeting next week as a target to provide updates on needs

Recap and Next Steps

- Discuss in more details to align on network capabilities and additional operational needs

Chatbox

**ACTIV, Therapeutics-Clinical Master Protocol Subgroup,
ACTIV-3 Writing Team Meeting, Meeting Minutes**

Monday, June 8th, 2020

Action Items

Action Items		
	Information	POC
1	Share the full ACTIV-3 master protocol document with companies attending the mAb Clinical Summit	Stacey Adam
2	Share any additional feedback from the companies to Jens Lundgren and Judy Currier before the summit	Stacey Adam

Notes

Opening

- Stacey Adam thanked the team for their hard work over the weekend on the master protocol.
- The completed master protocol will be submitted for CSRC review this afternoon.
- Feedback from CSRC is due back by Friday. Plan is to submit to FDA next week.

mAb Clinical Summit Update

- The mAb Clinical Summit is Jointly held by ACTIV and Operation Warp Speed
- Jens Lundgren and Jim Neaton will attend the summit to present the ACTIV-3 master protocol synopsis. Network representatives from PETAL and CSTN will attend as well.
- Stacey Adam reviewed the clinical summit agenda:
 - Governance and decision-making process: Consist of not only individual governance for each trial but also governance across trials. This governance entity will act as a neutral third party to review agents as they come in.
 - Regulatory perspective
 - Gating criteria
 - Presentation on protocols to get company feedback
 - Execution of protocols
 - Closing remarks: This will be a call to action for companies to come forward to partner. We are hoping to get verbal commitment to participate. We have 12 companies attending. 6-7 of them have good antibodies by end of the year.
- Stacey Adam has shared some early feedback from the companies with Jens Lundgren and Jim Neaton. The full protocol should address a lot of those questions. Stacey can share the full document with the companies to pre-empt their questions when available.

ACTIV-3 Full Master Protocol Update (Refer to Jens' Presentation)

- Jens Lundgren thanked the team for working on this: It was team building on speed - team members with different experiences and different background coming together. Jens

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acknowledged the joint effort and think team has arrived at a good product. Jens is looking forward to seeing the feedback.

- Hypothesis (Slide 2)
 - Right now, standard of care is Remdesivir. The master protocol allows it to change.
- Multi-arm two stage design (Slides 3-5)
 - End points are different at the interim and at final
 - Advantage of sharing control arm (i.e., pooling placebo across all treatments)
- Design feature (Slide 6)
 - Outcome at Stage 1: two ordinal outcomes at Day 5 (pulmonary+ and pulmonary). This is designed to protect activity.
 - Outcome at Stage 2: Time to recovery (more explanation later)
 - Extended follow-up to 90 days: As we learn more about the long-term health and mortality impact of the disease, team felt it is important to extend the follow-up duration to beyond the 28 days used currently.
- Graduation to stage 2 (slide 9)
 - If there is non-concordance with the two ordinal scales, the process is to go through DSMB review. There is good language in the master protocol document to help guide DSMB in this situation.
- Primary outcome – definition of recovery (Slide 10)
 - In certain settings, patients remain in the hospital for public health reasons but are not requiring hospitalized care
- Important secondary outcomes (Slide 11)
 - Composite of time to recovery and mortality through 90 days: ensure that primary outcome of mortality hopefully is in the same direction (seen in ACTT-1) but not formally described to do that
 - Time to sustained recovery: There is a clear realization that certain patients might not have fully recovered when they are discharged (i.e., some patients may be re-admitted). Team has refined the outcome to “continuously fulfilled the recovery definition for 28 days”.
 - Changes profile: Will collect get baseline titers on Day 1 and monitor decline / kinetics of antibody titers

ACTIV-3 Full Master Protocol Discussion

- Jim Neaton: Inclusion criteria changed over the weekend.
 - Jens Lundgren: We had a discussion around who to include in Stage 1, i.e., whether to include patients in Category 5 of the pulmonary ordinal scale at baseline. After some discussions, team ultimately decided to include. The only category not to include is

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Category 6. Patients shouldn't have those extrapulmonary conditions listed in Category 4 of the at time of entry in Stage 1.

- Yves Rosenberg: First of all, congratulations on putting the study together. One potential point we might have when it goes to DSMB review and implementation is related to the two scales. They are complementary but different. This might complicate data collection and interpretation. The consensus is to proceed with these two scales, but maybe there are other ways to comparing these scales to make things a bit straightforward.
 - Jens Lundgren: It would've been easier to have one. We don't know for sure which one to use to pick up activity. We can make a guess, or we can allow it to float and have co-equal scales to make decisions. We also received feedback from the mAb Steering Committee to have an "or" with the two scales, then lay out a plan in the "DSMB Guide" section on how to resolve non-concordance.
 - Jim Neaton: One scale would be preferable. There are good arguments on both sides. We will learn from trials we did; eventually we can remove one.
 - Yves Rosenberg: Are you concerned from site point view?
 - Jim Neaton: It will not impacting enrollment – if anything it has broadened enrollment. It will have impact on DSMB decision-making. For certain measures, such as oxygen requirement, the two scales are similar. There is a strong argument, given our state of knowledge, these conditions should be taken into account. Some of these outcomes would lead longer stay in hospital, and given primary outcome of this trial, those are important to consider in many respects.
 - Jens Lundgren: The CRF that would capture the information is already designed. It will not be extraordinary for the sites. They will only need to capture the conditions, and it would be computed centrally through the CRF.
 - Yves Rosenberg: I would recommend testing the before field implementation. I was referring to concerns with site enrollment – if it's different or complicated they might not consider participation.
 - Jim Neaton: We have attempted to make data collection simple. For conditions such as thrombotic events, renal failure, etc., whether they are ordinal outcomes or not, they will need to be considered and captured, as they will impact hospital stay. We have attempted to design data collection to be as simple as possible for the sites. That has not been an issue we've heard so far and the forms are very similar to these the ACTT-1 trial. I think there is an appreciation that these are being collected.
 - Jens Lundgren: The form is being field-tested. We are asking the same people who completed ACTT-1 to take a sample of the patients to complete these forms. The feedback we get is it's easy.
 - Yves Rosenberg: We would likely go to the sites to explain about data collection.
 - Jim Neaton: That's a valid point. It will require upfront training and communication for them to understand. That experience is important to guide us. This is new for all of us in terms of what information is important and needed.

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- Samuel Brown: There is a lot of enthusiasm from the sites to understand the novel complications that are extrapulmonary manifestations of this disease. I think Jim and Jens have done a good job to achieve a balance. Let the sites to keep track who's having these conditions and allow the team to understand how you would integrate these manifestations in a validated endpoint. To me, thinking from clinical perspective, this is good to acknowledge the enthusiasm to understand the manifestations and to understand the "bread and butter" oxygen-based outcomes. Sites don't have to do extra data manipulation if the CRF can capture in the backend. This is a great balance.

Next Steps

- Jens Lundgren: Protocol is undergoing final editing.
 - Jim Neaton: You will have it in two hours.
- Jens Lundgren: Although we are done with the document, there will be opportunities to make sure we all have a chance to carefully read the document to make sure everyone is happy.
- Judy Carrier: It's phenomenal to watch this team work together. Question about the clinical summit: Lots of comments have come back for both protocols. What's the best way to take the feedback from companies and respond to it?
 - Stacey Adam: Some of them about a quarter, will naturally be answered through presentation. If there's some natural way to incorporate the response in the presentation, it would be great. Some of them would come into Q&A. The remaining questions will be responded offline afterwards.
- Judy Carrier: We will allow combo, and companies will have appendices in the master protocol to give them the ability to customize. Maybe we need to articulate during the presentation that this is intended to be a collaboration.
- Sarah Read: Is the intention to provide a written response? A lot of questions are to around the rationale – it wouldn't be easy to address during the limited time.
 - Stacey Adam: For those, yes, we promised written responses – I would need the team's help to compile those.
- Yves Rosenberg: Are combos tested in stage 1 indefinitely or are they allowed to go through?
 - Stacey Adam: The guidance from the leadership is that if they meet the same bar as the mAbs can meet, they can enter the trial from the beginning.
 - Jens Lundgren: It's essentially one compound with multiple components. One scenario could be we find early on an active compound that works then move the field, then question is what if we add another compound into the combination. That becomes another discussion down the line.
 - Stacey Adam: There is already a summit being planned to tackle combinatoric approach to mAb agents. They understand that there will be a need. There are already a few companies with single agent that are combinations. The leadership would not want to exclude those.
 - Jens Lundgren: In the PALM study, one of the arms was a combinatory agent, right?

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- Jim Neaton: I think so. I don't see it being treated different. I think it's a different design if we want to combine different drugs.
- Jens Lundgren: We also allow several doses in Stage 1 to assess which to move to Stage 2.

Chatbox

From Samuel Brown to Everyone: 11:26 AM

Well done!

From Samuel Brown to Everyone: 11:46 AM

PALM had two combo Mabs, a single Mab, and RDV

From Libby Higgs to Everyone: 11:47 AM

Yes, REGN EB3 was a combination of 3 mabs, as was Zmapp. We did not study Rem + any of the mabs

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) received status updates on the ACTIV-2 and ACTIV-3 trials and discussed other topics elevated for its consideration. Dr. Stacey Adam also noted that the follow-up meeting on the planned vaccination post-mAb study is scheduled for Thursday, February 18 at 10:00 am Eastern Time; any TOC members who have not received an invitation can request one from Dr. Adam.

The TOC agreed to initiate discussions between (b) (4) and the ACTIV-2 team but decided to hold on connecting (b) (4) with the ACTIV-3 team. The TOC also agreed to initiate discussions between (b) (4) and the ACTIV-3 team to advance (b) (4)'s protease inhibitor.

Trial Accrual and Status Updates

ACTIV-2

ACTIV-2 has activated 104 sites (b) (4) arm and three enrolling to Version 3 of the protocol) and (b) (4) ACTIV-2 randomized its first patient to Version 3 of its protocol on February 10. Efforts continue to increase demographic diversity among patients.

The ACTIV-2 team will meet with FDA on February 11, 2021 to (b) (5). Initial guidance received from FDA suggested (b) (5). FDA has also indicated (b) (5) and the ACTIV-2 team (b) (5). Dr. (b) (6) noted that FDA's (b) (5).

Dr. (b) (6) noted (b) (5).

ACTIV-3

ACTIV-3 has activated 54 sites (b) (4), (b) (4) and has now (b) (4). Dr. (b) (6) noted that the DSMB will meet on March 1 (b) (4), and perhaps also to conduct (b) (4). The ACTIV-3 team is onboarding the (b) (4) and activation of ex-U.S. sites continues, although the sites in Poland are the only ex-U.S. sites currently enrolling patients.

Topics for Discussion

Updates on Potential Pragmatic Trial (“ACTIV-6”)

PCORnet has been selected to lead ACTIV-6 and plans are underway to engage NIH’s SIREN and CONNECTS networks to conduct the trial. Funding plans, which have not yet been finalized, would include support for expansion of PCORnet to include 200 overall sites. Vanderbilt University will serve as the ACTIV-6 data coordinating center and will build a remote reporting system for the trial based on its previously developed TreatNOW system. The first drug to be tested in the ACTIV-6 study will be ivermectin; a company has already agreed to provide the drug supply as well as placebo, and agreements are being drafted. Daily logistics meetings will soon begin to ensure that the process moves quickly and will continue until trial launch. Dr. Adam will contact Dr. Peter Stein at FDA to confirm which regulatory group will oversee this trial. A description of study assumptions and budget will be presented to USG Therapeutics imminently. Once ACTIV-6 launches, the TOC will oversee it along with PCORnet representatives and ACTIV-6 leadership.

Given the intention to combine multiple clinical networks to conduct ACTIV-6, Dr. Sam Bozzette encouraged the trial planning group to consider potential strategies for reducing the number of placebo patients needed to adequately power the trial.

Agent Evaluation

(b) (4)

The Agent Selection Committee (ASC) previously reviewed (b) (4) provided further data and the ASC widely agreed that the agent appears promising. More phase I and dosing data are needed but the ASC (b) (4) will also be providing a brief on how its (b) (4) expected to be able to enter ACTIV-2 by late March/early April. The TOC approved advancing this agent for discussion with ACTIV-2 but decided not to initiate discussions between (b) (4) and ACTIV-3 until initial Ab readouts are reviewed by the ACTIV-3 DSMB on March 1.

(b) (4)

The ASC has reviewed readouts from (b) (4) and determined that it appears promising as a potential ACTIV-3 agent—it is unsuitable for ACTIV-2 because it requires continuous (b) (4). Dr. (b) (6) emphasized the importance of ensuring that this agent does not exhibit antagonistic effects (b) (4) or ACTIV, to assess this possibility. The TOC agreed to advance this agent.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Samuel Bozzette, MD, PhD, Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)

Elizabeth Church, PhD, Deputy Director, Therapeutics Research Program, Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), NIH

Judith Currier, MD, Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)

Ann Eakin, PhD, Senior Scientific Officer, Concept Acceleration Program, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)

Emily Erbeling, MD, MPH, Director, Division of Microbiology and Infectious Diseases, NIAID, NIH

David C. Goff, MD, PhD, Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI), NIH

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, Global Health Science Advisor, NIAID, NIH

James P. Kiley, PhD, Director, Division of Lung Diseases, NHLBI, NIH

Peter Kim, MD, Director, Therapeutics Research Program, Division of AIDS (DAIDS), NIAID, NIH

H. Clifford Lane, MD, Deputy Director for Clinical Research and Special Projects, NIAID, NIH

Jens D. Lundgren, MD, Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT

Gilbert (Lynn) Marks, MD, Senior Adviser to BARDA, Office of the Director

James D. Neaton, PhD, ACTIV-3 Chair and Professor of Biostatistics, University of Minnesota

Sarah Read, MD, Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)

Erica Ollmann Saphire, PhD, Professor, La Jolla Institute for Immunology

David (Davey) Smith, MD, Professor of Medicine, U. California, San Diego

Peter Stein, MD, Director of Office of New Drugs, CDER, FDA

OTHER INVITED ATTENDEES

Col. Deydre Teyhen, DPT, PhD, Director of Therapeutics, Operation Warp Speed

STAFF

Stacey Adam, PhD, Director, Cancer, Foundation for the NIH (FNIH)

David Wholley, MPhil, Senior Vice President of Research Partnerships, FNIH

Helen Q. Chen, Consultant, Deloitte

Evan Appell, Consultant, Deloitte

Nada Saleh, Consultant, Deloitte

Lucas Smalldon, MA, Writer, Rose Li and Associates, Inc.

Appendix B: Chat Transcript

Libby Higgs: Thanks for organizing Stacey

Emily Erbelding: no reservations

Lynn Marks: sounds like a good idea

Davey Smith: no reservations

Jim Kiley, NHLBI: Will this go to activ3?

Jim Kiley, NHLBI: Agree with Cliff's point

Ann Eakin: Worth mentioning that (b) (4) has an oral protease inhibitor following - Ph1 in March?

Emily Erbelding: no reservation

High-Level Meeting Summary

The ACTIV-3 Team convened to present an outline of and receive initial Steering Committee (SC) feedback on the ACTIV-3 master protocol, designed to test mAbs and subsequently additional compounds in inpatient populations. The team intends to have a full draft of the ACTIV-3 protocol by Monday June 8, a revision for NIAID CSRC review on June 11, and a submission rapidly thereafter for FDA. The protocol is expected to launch in late June or early July within the INSIGHT network with additional support from the VA, ACTG, PETAL, and CTSN.

ACTIV-3 Master Protocol Overview

Dr. Jens Lundgren presented an overview of key decisions and open questions in the ACTIV-3 protocol. The protocol will test the hypothesis that mAbs with Standard of Care (SOC) will accelerate time to recovery among hospitalized patients with COVID-19 compared to mAb-placebo with SOC (SOC is remdesivir and time to recovery is defined as hospital discharge over a 90-day follow-up period; readmissions may be handled as a secondary outcome).

- **Design:** multi-arm multi-stage (MAMS)
 - *Multi-arm:* test many treatments at the same time
 - *Multi-stage:* use interim 'lack-of-benefit' analyses to identify reasons to continue to investigate an approach
 - *Stage 1 (interim):* identify early activity signal by Day 5 to assess whether investigational agents should proceed to Stage 2
 - *Stage 2 (final):* assess clinical efficacy over course of disease with respect to time to recovery
- **Approach to randomization:** consistent with other ACTIV protocols, each investigational treatment against control arm (pooled across all patients in the control group contemporaneously enrolled)
- **Trial entry:** three pathways for agents to enter trials:
 - No compelling phase I data → Phase I study completed in ACTIV-3
 - Available and compelling Phase I data (based on SC assessment) → enter Stage 1
 - Compelling Phase 1 + preliminary compelling efficacy data from other sources → enters Stage 2
- **Outcome measures:** 7-category ordinal outcome of disease stage after 5 days with early capture if treatment works; three approaches to criteria for graduation are under consideration:
 - Based on INSIGHT 013, criteria would include pulmonary and extra-pulmonary symptoms, reflecting inflammation and coagulation linked to COVID-19 and responsiveness of related biomarkers to remdesivir

Category	Description
1	No limiting symptoms due to COVID-19
2	Limiting symptoms due to COVID-19
3	Moderate end-organ dysfunction
4	Serious end-organ dysfunction
5	Life-threatening end-organ dysfunction
6	End-organ failure
7	Death

- Based on PETAL, criteria would focus exclusively on pulmonary symptoms, reflecting the lungs as the primary organ affected by COVID-19 and the responsiveness of oxygenation levels to remdesivir
- Accept scoring for *either* pulmonary or extrapulmonary criteria
- **Secondary outcomes:** primary second outcome is safety, with other outcomes including mortality; composite of recovery and mortality; ordinal outcome at days 1, 3, 7, 14, and 28; change in neutralizing antibodies at days 1, 3, 7, 28, and 90; and effect on subgroups

Each stage of ACTIV-3 adopts key design features from ACTT1 and ACTT2 as well as from ACTIV-1. However, ACTIV-3 extends follow-up time from 28 days (in ACTT) to 90 days in order to capture the incremental mortality effect typically seen in patients with severe clinical presentations of COVID-19.

Features	Stage 1	Stage 2
Target population	Patients hospitalized for medical care who have had COVID-19 symptoms $\leq$ 12 days, and who do not have life-threatening organ dysfunction or organ failure	Same as in stage 1, second also including patients with life-threatening organ dysfunction or organ failure
Efficacy outcome used	Ordinal outcome at day 5	Time to recovery
Follow-up	90 days	90 days
Effect size and power	OR = 1.61 for favorable outcome, type 1 error = 20% (1-sided), & power = 95%	25% increase in rate of recovery, type 1 error = 5%, & power = 90%
Sample size for one or two successful candidates introduced together	300 or 450	1,812 or 1,218 (of which 300 or 450, resp. from stage 1)

Discussion

Criteria for Graduation: Pulmonary, Extrapulmonary, or Either

SC members discussed tradeoffs between measurements of pulmonary and extrapulmonary symptoms. They wondered if extrapulmonary symptoms that emerged simultaneously with initial treatment would effectively undermine the study before it had truly begun. Although Dr. Lundgren assured them that the protocol is designed to capture improvement over time (so that, for example, a case of myocarditis that surfaced simultaneously with a first infusion on Day 1 would not count against an agent if the case improved by Day 5), participants noted that pulmonary symptoms might nonetheless respond to treatment more *rapidly* than extrapulmonary symptoms and thus may generate a clearer signal at Stage 1.

However, SC members recognized that excluding extrapulmonary symptoms may lead to an incomplete picture of treatment effectiveness. They also noted that too little is known about COVID-19 to determine confidently which clinical dimensions matter most. Thus, they agreed that accepting incremental progress in *either* pulmonary *or* extrapulmonary symptoms would best assess specific agents and at the same time shed greater light on endpoints themselves.

Dr. Lundgren acknowledged that the assessment of some extrapulmonary symptoms (e.g., pericarditis) depends on clinical judgments that cannot be easily confirmed by fluid samples. He noted that randomization will compensate for any of these judgments' effects.

Time to Separation

SC members considered whether separation between trial and control groups would emerge in the timeline envisioned by the protocol. Dr. Lundgren noted that ACTIV-3 seeks incremental effects beyond improvements seen in remdesivir and that in ACTT1, remdesivir achieved separation within five days. SC members suggested that the timeline observed for remdesivir may depart in small but significant ways from the effects of mAbs, which are not yet known, and thus that it may be worthwhile to move the Stage 1 measure from Day 5 to Day 7 or 8. However, Dr. Jim Neaton noted that the threshold for progression to Stage 2 is fairly liberal,

with an alpha of 0.3. This setting should allow any promising agents to move to Stage 2 and help reveal which predict the ultimate endpoint of time to recovery.

Impact of Inclusion Criteria on Enrollment

In response to questions from the SC, Dr. Lundgren clarified that while inclusion criteria for Stage 1 depart from ACTT1 and ACTT2 by excluding patients with life-threatening illness, this departure should not result in slower enrollment than those trials have achieved. Eighty to ninety percent of newly admitted COVID-19 patients meet the narrower criteria for Stage 1, and hospitals treating COVID-19 patients have four times as many medicine beds as intensive care beds. The limitation is necessary to generate signals on the ordinal outcome scale used in Stage 1 but is subsequently removed for patients in Stage 2.

Data Collection on Natural Immunity

The SC discussed the importance of assessing the impact of mAb infusions on natural immunity. Dr. Lundgren noted that virology data collected within ACTIV-3 is not useful for this assessment: twenty-two to thirty-three percent of hospitalized patients' nasopharyngeal swabs are negative for replicating virus and sampling of the lower respiratory tract, where the virus *is* replicating, would not be conducted. ACTIV is considering several ways to collect long-term data. ACTIV-3 will measure changes in neutralizing antibodies over the 90-day study period to reveal any blunting of t-cell response, while ACTIV-2 will include a 24-week follow-up with outpatients. ACTIV is also drafting a protocol for a five-year follow-up for recovered patients from any ACTIV trial as well as new entrants. Dr. Janet Woodcock noted that tens of thousands of people are receiving convalescent plasma who could be enrolled in such a follow-up study.

Harmonization of Endpoints

SC members observed that many sponsors are using ordinal scales with different endpoints. Dr. Lundgren noted that changes in endpoints have typically been driven by evolving knowledge of COVID-19. For example, the involvement of extrapulmonary symptoms was not clear for several months and the 28-day timeline employed in ACTT1 was subsequently revealed to be far too short. Researchers are working to collect and pool data to compensate for these shifts. ACTIV-3 will collect information that can support comparison to other studies' endpoints and aid future meta-analyses. Dr. Carl Garner described an industry effort to pool treatment and control data from as many studies as possible in a single database (likely to be run by ^{(b) (4)}). Dr. Stacey Adam notified participants that NIH leadership considering how to share this type of data and is exploring whether sharing in this type of database would meet requirements for public accessibility.

Update on mAb Summit

All members of the SC are invited to the mAb summit taking place on June 9. Four representatives from each trial committee have also been invited (generally the network lead, principal investigator, head statistician, and one other member of their choosing). The most up-to-date drafts of protocol synopses were shared with attending companies earlier this week.

Appendix A: Participants List

MEMBERS – STEERING COMMITTEE

Samuel A. Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), NIH*

Joan Butters, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

William Erhardt, MD, *Special Advisor, Operation War Speed*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Rachel Harrigan, *Special Advisor, Operation Warp Speed*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Marina Kozak, PhD, *Health Scientist, Biomedical Advanced Research and Development Authority (BARDA)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

Gilbert “Lynn” Marks, MD, *Senior Adviser to BARDA, Office of the Director*

Karen Price, PhD, *Senior Research Advisor, Statistical Innovation Center Lead, Eli Lilly and Company*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Janet Woodcock, MD, *Therapeutics Lead, Operation Warp Speed*

ACTIV-3 Team

Neil Aggarwal, MD, *Branch Chief, National Heart, Lung, and Blood Institute (NHLBI), NIH*

Abdel G. Babiker, PhD, *Professor of Epidemiology and Medical Statistics, University College London*

Emilia Bagiella, PhD, *Professor, Mount Sinai School of Medicine*

Samuel M. Brown, MD, *Associate Professor of Internal Medicine, University of Utah*

Christina Chang, PhD, *Senior Research Fellow in Clinical Trials and Cohorts, University of New South Wales Sydney*

Annetine Gelijns, PhD, *Professor, Mount Sinai School of Medicine*

Birgit Grund, PhD, *Associate Professor of Statistics University of Minnesota*

Catherine “Terri” L. Hough, MD, *Professor of Pulmonary, Critical Care, and Sleep Medicine, University of Washington*

Joseph Koopmeiners, PhD, *Associate Professor and Interim Division Head, Division of Biostatistics, University of Minnesota*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT*

Michael Matthay, MD, *Professor of Medicine, University of California, San Francisco*

Alan Moskowitz, *Professor of Population Health Science and Policy, Mount Sinai and Leadership Team, CTSN*

James D. Neaton, PhD, *Professor of Biostatistics, University of Minnesota and Principal Investigator, INSIGHT*

Jessica Overbey, DRPH, *Assistant Professor, Icahn School of Medicine at Mount Sinai*

Andrew Phillips, PhD, *Professor of Epidemiology and Biostatistics, University College London*

Cavan S. Reilly, PhD, *Professor of Biostatistics, University of Minnesota*

Lora Reineck, MD, *Program Director, National Heart, Lung, and Blood Institute (NHLBI), NIH*

Wesley Self, MD, MPH, *Associate Professor of Emergency Medicine, Vanderbilt University*

Taylor Thompson, MD, *Medical Director and Co-Principal Investigator, ARDS Network Clinical Coordinating Center*

David M. Vock, PhD, *Associate Professor of Biostatistics, University of Minnesota*

INVITED PARTICIPANTS

John Farley, MD, MPH, *Director of Office of Infectious Diseases, CDER, FDA*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

00:25:01 Karen

If you do not already, you might consider stratifying by duration since symptom onset (e.g., ≤ 5 , > 5 , which is what is in ACTIV-2 I believe)

00:26:43 Carl's Lilly iPad

Prudent to consider given many patients 12-days post symptom onset will be coming down on the ordinal scale pretty rapidly.

00:31:24 (b) (6)

If the group goes with the broader outcome, it could take a while for some of the extrapulmonary manifestations (e.g., DVT) to resolve

00:32:38 Libby Higgs

To Sam's point that was part of the concern.

00:37:37 Terri Hough

Significant myocarditis or PE will be associated with hypoxemia and/or shock. We could count that.

00:38:29 FARLEYJ

Is (b) (4) required or a stratification covariate? Availability in different settings may be a challenge in the near future.

00:39:08 FARLEYJ

Are viral NP samples being collected?

00:39:30 (b) (6)

Would suggest having cake and eating it too: go with "OR"

00:48:05 Libby Higgs

(b) (4) is considered SOC at this time so every should have it.

00:48:40 Samuel Brown

Will an OR approach complicate alpha spending in stage 1?

00:50:54 (b) (6)

? to steering committee: how much should we care about harmonization across ACTIV 1-2-3?

00:52:35 Lisa LaVange

ACTIV-2 and -3 are studying the same agents in different populations, so harmonization would be good. And ACTIV-1 and ACTIV-3 are studying different agents in the same population, so also a call for harmonization. Both get my vote, but ACTIV-1 has the particular characteristic of not having a phase 2 screening stage, unlike the other two.

00:55:58 Libby Higgs

I think we should harmonize the phase 3 efficacy endpoints for inpatient studies e.g. time to recovery. And we should harmonize the outpatient efficacy endpoints.

00:56:52 (b) (6)

We may need an "endpoint summit" in addition to the "mAb summit."

00:59:15 Stacey Adam

Sam agreed on endpoints, if nothing else internally

01:00:24 (b) (6)

"steering committee" + protocol leadership? for the endpoint summit?

01:00:49 Stacey Adam

Yes

01:04:56 FARLEYJ

Peter and John recommend submitting the protocol synopsis to FDA for Pre-IND advice. This would facilitate endpoint discussion internally and that would be value added.

ACTIV, Therapeutics-Clinical Master Prioritization Sub Group

Working Group Meeting 3, Key Takeaways

Monday, April 20th, 2020

Action Items

Action Items		
	Information	POC
1	Share the (b) (4), (b) (5) survey of clinical sites	Stacey Adam
2	Modify (b) (4), (b) (5) timeline and action items list	Co-Chairs, Sub-Chair, Stacey Adam
3	Determine who will (b) (4), (b) (5)	Full WG
4	Come prepared to tomorrow's Subgroup meeting to discuss components to include in (b) (4), (b) (5) from existing protocols	Full WG
5	Start sketching out high level timelines for (b) (4), (b) (5), etc.	Co-Chairs, Sub-Chair, Stacey Adam

Key Takeaways

- Group consensus on taking a hybrid approach to getting (b) (4), (b) (5) timelines needed; the group was also in consensus on (b) (4), (b) (5) to add the highest priority (b) (4), (b) (5) from our prioritization
- Group consensus was to (b) (4), (b) (5) (s) in parallel the (b) (4), (b) (5)
- Reminder to all that part of the group's remit is to think big. Think about the bigger picture and advise ACTIV leadership.
- Group consensus that ACTIV will ask sites to come (b) (4), (b) (5); "take it or leave it" approach.
- Suggestion for simplified (b) (4), (b) (5) (something fast and painless for sites to open and collect data), (b) (4), (b) (5)
- Feedback on action items list and timelines, including shortening days for (b) (4), (b) (5) and adding additional days for (b) (4), (b) (5)

(b) (4), (b) (5) steps and timeline

- Co-Chairs and Sub-Chair worked on (b) (4), (b) (5) action items list and timeline – (b) (4), (b) (5)
- Group discussion on (b) (4), (b) (5) and timeline – reviewed the assumptions on slide.

Monday, April 20th, 2020

- What would it look like if we broke down timelines for (b) (4), (b) (5)
 - Best case scenario for the (b) (4), (b) (5) for short-term speed—completion in 31 days. Worst case scenario is 47 days if we adhere to the steps outlined above.

ACTT protocol

- Concern about ACTT protocol
 - Not set up exactly like a (b) (4), (b) (5)
 - So, in our action items list, Step #2 about (b) (4), (b) (5).
 - Suggestion to write ACTT3 in a way similar to ACTT2 for the first few drugs and then in parallel work on (b) (4), (b) (5). This will allow us to focus not just on short term needs, but where we will go in the future.
 - ACTT3 can focus on the (b) (4), (b) (5) that the WG picks. Then we can put ACTT aside and focus on (b) (4), (b) (5). However, we will need to (b) (4), (b) (5) across the two to allow for data comparison.
- For group's awareness: ACTT2 is being submitted to the FDA today or tomorrow, and a fast turnaround is expected. They plan to open ACTT2 at (b) (4), (b) (5).
 - The enrollment rate for ACTT is (b) (4), (b) (5). This is the sample size they need for ACTT2. Not certain if ACTT2 will open at all the same sites but could almost be fully enrolled by the time ACTT3 ACTIV master protocol is ready to be implemented.
 - Primary analysis will be in first week of May. Our best-case scenario for ACTT3 is mid-to-late May.
- The group needs to grapple (b) (4), (b) (5)
- The beauty of grafting onto ACTT is that they have (b) (4), (b) (5). But if you have to start with new sites, it will slow down efforts efforts. Getting sites up is not trivial.

Implementing in New Sites, Engaging Networks, and Thinking Big

- For (b) (4), (b) (5) implement in new sites?
 - During last discussion, WG members suggested (b) (4), (b) (5). We should not regress.
 - When monoclonals or first antivirals come, we don't know where we will need to be in 3 months.
- Are we thinking big enough?

ACTIV, Therapeutics-Clinical Master Prioritization Sub Group
Working Group Meeting 3, Key Takeaways

Monday, April 20th, 2020

- Part of the group's remit is to provide ACTIV leadership advice and feedback. We have a short-term remit, but we need a bigger picture.
- Many people in the group resonate with need to think big, and this idea supported by (b) (4), (b) (6) ACTIV leadership is looking to this expert WG to advise.
- (b) (4), (b) (5) Everything is on the table.
- Intention was not to keep to one network but to identify the fastest way to (b) (4), (b) (5) WG needs to assess the fact that each network has its own (b) (4), (b) (5) to the roll out to another network and another network – or do we do this all at once?
- (b) (4), (b) (5) to put their sites into our trials.
- What number of sites is optimal? Need for a large network.
 - (b) (4), (b) (5) Formidable challenge.
 - Suggestion for certain trials to be conducted in certain subsets of sites
 - (b) (4), (b) (5)
 - If there are (b) (4), (b) (5) running, we can pick 100 that are “hottest” in a given time. The sites just need to be up and ready.
 - Question of whether we have enough for sites to do if there are (b) (4), (b) (5)
 - We have a very long list of therapeutics, (b) (4), (b) (5)
- Engaging networks
 - Suggestion that networks should contribute sites but for the operating machinery of trial to belong to the trial and not to be distributed to networks
 - (b) (4), (b) (6); as someone who leads a network, agrees. (b) (4), (b) (5) We can borrow the best and make into something new that everyone feels they are a part of.
 - ACTIV also has the opportunity to (b) (4), (b) (5)

ACTIV, Therapeutics-Clinical Master Prioritization Sub Group
Working Group Meeting 3, Key Takeaways

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- We could approach a network ask them to participate. The networks can tell us yes or no. There will be a lot of sites that won't want to be left behind because we'll have access to a lot of molecules that they'll want for their patients.

Therapeutics-Clinical Working Group informing Clinical Trial Capacity efforts

- The Therapeutics-Clinical group needs to make key decisions around what network will look like and provide guidance to the Clinical Trial Capacity Working Group.

- The CTC Working Group is (b) (4), (b) (5)

- Once the Therapeutics-Clinical can provide more answers, (b) (4), (b) (5)

On Writing (b) (4), (b) (5)

- Companies (b) (4), (b) (5)
- (b) (4), (b) (5) With interactive response technology, especially for complex adaptive trials, there's a lot of programming around that.
 - (b) (4), (b) (6) - we are under the assumption that we don't (b) (4), (b) (5)
 - (b) (4), (b) (5)
 - Need to decide how quickly those waves start - (b) (4), (b) (5)
- Need to make timeline for (b) (4), (b) (5)
 - There are ways to make the (b) (4), (b) (5) easier to get started.
 - Ex) Hospitalized and pre-hospitalization can be (b) (4), (b) (5)
 - (b) (4), (b) (5) is hard to have in the beginning, but we don't have to have everything ready always at the beginning.
- Clarification that our Master Protocol WG (b) (4), (b) (5)
- Need to consider (b) (4), (b) (5) - highlight this in timelines to start very early, in parallel
- (b) (4), (b) (5)

ACTIV, Therapeutics-Clinical Master Prioritization Sub Group

Working Group Meeting 3, Key Takeaways

Monday, April 20th, 2020

- Suggestion to add additional days in writing of (b) (4), (b) (5) - that discussion alone can take a few hours. There are a number of things we need to work through in writing protocol.
- Anything to prepare for (b) (4), (b) (5)
 - A lot of (b) (4), (b) (5) for ACTT1 and ACTT2, but not sure if they're ready.
 - There's a (b) (4), (b) (5). Need to be careful on what we want to choose. Need to make sure it's consistent between the local and central.

(b) (4), (b) (5) Assumptions Discussion

- Regarding "Network selected already has CIRB and DSMC selected and ready to review," group consensus that we are asking sites (b) (4), (b) (5)
- Regarding "Use of parts of existing master protocols as templates," group consensus that ACTIV will do some (b) (4), (b) (5)
 - (b) (4), (b) (5) will operate in real life.
 - ACTT will show how it performs, and we need to (b) (4), (b) (5)
 - Suggestion for interim solution: think about (b) (4), (b) (5) WG should think of endpoints that resonate with clinicians who have to make decisions about individual patients.
 - Need to think about how to simplify trials.
- According to (b) (6), by end of this week, FDA hopes to have its guidance out on trial endpoints and harmonization.
- Suggestion that as we're thinking about (b) (4), (b) (5)
- Importance of streamlining as much as possible
- Suggestion to offer some sites to do more complex evaluations and provide an optional component

Next Steps

- (b) (4), (b) (5)
 - Shorten timelines: under 30 days for best case scenario and under 45 for worst case
- (b) (4), (b) (5)
 - Add more time because we may be writing something a bit more complex and may have a few other things to get in place/contracted like (b) (4), (b) (5)
 - (b) (4), (b) (5), and people will have to "take it or leave it." Suggestion to have a few companies involved at the beginning.

ACTIV, Therapeutics-Clinical Master Prioritization Sub Group
Working Group Meeting 3, Key Takeaways

Monday, April 20th, 2020

Chatbox

From (b) (6) to Everyone: 02:21 PM

are we thinking big enough with respect to the scope of the trial per se?

From (b) (6) to Everyone: 02:34 PM

Will the (b) (4), (b) (5) be concurrent to this?

From (b) (6) to Everyone: 02:35 PM

Agree with the comment on (b) (4), (b) (5)

From (b) (6) to Everyone: 02:40 PM

Do we need to get (b) (4), (b) (5) ready?

From (b) (6) to Everyone: 02:48 PM

When is the FDA guidance for (b) (4), (b) (5) going to be released? Need to align with (b) (4), (b) (5).

High-Level Meeting Summary

The Monoclonal Antibody (mAb) Subteam of the Therapeutics Clinical (TX-Clinical) WG's Agent Prioritization Committee (APC) continued refining the proposed (b) (4) to admit candidate SARS-CoV-2 neutralizing mAbs for testing under the ACTIV-2 (outpatient) master protocol. A representative from the (b) (4) and provided additional feedback for the Subteam's consideration.

Adjustments to ACTIV-2 (b) (4)

The TX-Clinical WG recommended three key refinements to the proposed ACTIV-2 (b) (4) for SARS-CoV-2 mAbs to move into Phase II studies: (1) (b) (4); (2) (b) (4); and (3) (b) (4). Revised (b) (4), developed by Drs. (b) (4), (b) (6) and (b) (4), (b) (6), were reviewed by the mAb Subteam, resulting in adjustments to the following categories:

Potency

Supporting data (b) (5)

(b) (5), the Subteam adjusted (b) (5)

Participants discussed (b) (5)

(b) (5)

(b) (5) The Subteam agreed (b) (5)

(b) (5)

Duration of Exposure to Adequate Antibody After Dosing

Referencing half-life criteria established by the (b) (4)

(b) (5), Dr. (b) (6) expressed (b) (5)

(b) (5)

(b) (5). Participants also considered whether (b) (5)

(b) (5)

Dr. (b) (6) recommended (b) (5)

(b) (5)

Percent Inhibition

Dr. (b) (6) expressed (b) (5)
(b) (5) Participants agreed that
(b) (5)
Therefore, (b) (5)

Dose/Route of Administration

For a Phase II study, participants agreed (b) (5)

Therefore, (b) (5)

Safety

Dr. (b) (6) recommended (b) (5)

Participants (b) (5)
Therefore, they
agreed (b) (5)

Developability and Scale-Up

Participants agreed that minimum criteria should include characteristics (b) (5)

Participants agreed (b) (5)

Additional Considerations for Minimum (b) (4)

Dr. (b) (6) inquired whether (b) (4) should consider (b) (5)

While
participants agreed (b) (5)

(b) (5)

. Moreover, because it is

(b) (5)

Participants agreed to preserve all other criteria from Dr. (b) (6) previous (b) (4) as 'nice-to-know' information, which can then be used to prioritize candidates, if necessary.

(b) (4)

Effort

Dr. (b) (6) briefed the mAb Subteam on parallel mAb therapeutic efforts supported by the (b) (4). Led by Dr. (b) (4), (b) (6) of the (b) (4) performs a battery of standardized, blinded assays to assess antibody properties, including potency, inhibition, pseudovirus assays, live virus assays, epitope binding, and structural biology.

Insights and Considerations for ACTIV-2 from (b) (4) Observations

mAb Cocktails

Dr. (b) (6) reported that some data suggest viral mutation escape issues may intensify the need for combination therapies, which are the focus of the (b) (4) effort, and inquired whether the Subteam has considered (b) (4). She recommended (b) (5).

While the mAb Subteam considers mAb cocktails desirable, the (b) (4) do not currently address them. Dr. (b) (6) suggested that the 'nice-to-know' information indicate that for mAb cocktails, each individual mAb (rather than the entire cocktail) must meet the (b) (4).

Effectorless Antibodies and ADEs

Dr. (b) (6) probed the Subteam's thinking about effectorless antibodies, given known risk for ADE and recent published reports using convalescent plasma treatments. Dr. (b) (6) expressed interest in a tractable model comparing effectorless mAbs outside of a clinical trial. However, Dr. (b) (6) expressed concerns about adequate detection of ADEs using in vitro data, and Dr. (b) (6) agreed it was impossible to completely eliminate ADE risk through preclinical models.

Disease Enhancement

In addition to efficacy, Dr. (b) (6) suggested it may be interesting to consider data regarding observed ADEs. Dr. (b) (6) agreed characteristics of disease enhancement warranted consideration, noting that at present, the ACTIV-2 protocol proposes only monitoring, and not

characterization, of disease enhancement. She further explained ACTIV-2 includes both clinical endpoints (e.g., symptom improvement) and virologic response endpoints, with the goal of learning (through the course of the study) what virologic response predicts in terms of clinical outcomes. However, given the uncertainty of virologic response, it is not currently intended as a Phase III (b) (4)

Patient Population for Phase I Data

Dr. (b) (6) inquired whether ACTIV preferred Phase I data from healthy volunteers or infected patients, suggesting that Phase I studies performed in infected patients may provide data on disease enhancement (depending on viral burden). While Dr. (b) (6) agreed in principle and noted FDA's preference for Phase I studies in infected patients; however, he felt that Phase I sample sizes likely will be insufficiently powered to detect ADEs unless they occur at very high frequency.

Next Steps

Dr. (b) (6) will circulate a final draft of (b) (4) to the mAb Subteam for approval. Once approved, the final draft will be presented at the next NIH Clinical Summit. Dr. (b) (6) will provide any feedback from the Summit to the mAb Subteam. She also expressed interest in the mAb Subteam continuing to act as a Review Committee once candidate mAbs are submitted for consideration in ACTIV-2. Dr. (b) (6) encouraged Subteam members to participate in scoring those candidates.

Appendix A: Participants List

Andrew Adams, PhD, *Chief Scientific Officer, RNA Therapeutics, Eli Lilly*

Sebastian Breuer, PhD, *Lab Head HTS & Project Leader, Roche*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, U. California, Los Angeles (UCLA)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Flavius Martin, PhD, *Vice President, Amgen*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Amanda Peppercorn, MD, *Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)*

Sarah Read, MD, *Deputy Director, Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) (TX-Clinical WG Co-chair)*

David (Davey) Smith, MD, *Professor of Medicine, U. California, San Diego*

Randy Tressler, MD, *Medical Officer, NIAID*

INVITED PARTICIPANT

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

Kelly E. Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

ACTIV, Therapeutics-Clinical Master Protocol Subgroup,
ACTIV-2-3 Writing Team Joint Meeting, Meeting Minutes

Thursday, June 4th, 2020

Action Items

Action Items		
	Information	POC
1	Share with this group feedback from companies after the mAb Clinical Summit	Stacey Adam
2	Continue discussion around harmonizing ACTIV-2 and ACTIV-3 studies, including setup to share learning across studies, sharing placebo recipient	Jens Lundgren / Tim Neaton / Judy Currier

Notes

Opening

- Intent of this meeting is for ACTIV-3 Writing Team to provide an overview to ACTIV-2 sub team in order to flab synergy and harmonization between the two master protocols.
- Opportunity to discuss any questions Jens wants input for.
- (b) (4) colleagues have interest in participating in the inpatient study – they are here to provide company feedback.

ACTIV-3 Synopsis [Refer to Jens' Presentation]

- Slide 1: Simplified hypothesis
 - Treatment / placebo would be added onto Remdesivir (base of standard of care)
 - Intend to provide Remdesivir to the sites in the study
- Slide 3: Emphasizing the approach to use “lack-of-benefit” analysis at the interim
- Slide 4: Multi-arm two-stage design
 - Stage 1 identifies activity– interim is designed for early activity signal
 - Stage 2 identifies efficacy – assess clinical efficacy over the course of disease
- Slide 6: Key design features
 - Patient population
 - Stage 1 – attempted to capture patients early on before antibody production
 - Stage 2 – expand the inclusion criteria
 - Efficacy: Team aligned on 90 days follow-up (rather than 60 days). This is different from ACTT-1 to account for duration of patient recovery for this patient population
 - Sample Size: Stage 2 sample size is front-loaded with Stage 1 patients
- Slide 7: Ordinal outcome and timing are under discussion

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- Team aligned on Day 5 for assessment. mAb effect might not be immediate so it shouldn't be too early after enrollment. Effect may be transient to miss the effect. Likely, separation between mAb and placebo is largest during the first 5 days.
- Using 7 categories of ordinal outcomes. Team is having ongoing discussion on what they entail, including key non-pulmonary manifestations (e.g., thrombosis and dialysis).
- Slide 9: Projection with the assumption that everything progresses through stages
 - Different doses are considered as different treatments in Stage 1. We are assuming that only one dose will move onto Stage 2.
 - Patients in Stage 1 are contributing to sample size in Stage 2.
- Slide 11: Treatment may enter trial in one of three ways
 - No Phase I data – Phase I to be done within the trial, outlined in an appendix section of the master protocol
 - With Phase I data – Enter into Stage 1; DSMB to review safety data
 - With safety and preliminary efficacy data – Enter directly into Stage 2
- Slide 16: Next steps and timeline

Discussion and Feedback

- Lisa LaVange: Phase II outcome is a 7-level scale - which is different from ACTT-1
 - Jens Lundgren: In ACTT-1, it's an 8-pt scale. Yes – the primary outcome of the 8-pt scale has been changed due to issue for time to recovery. This is compatible with the INSIGHT 013 protocol.
- Lisa LaVange: Day 5 is what we settled on?
 - Jens Lundgren: Yes - after extensive discussion today, and with input from ACTT-1 statisticians.
- Judy Currier: We are assessing improvement beyond Remdesivir?
 - Jens Lundgren: Treatment or placebo is added onto the base of Remdesivir. We would need to make a determination on whether the patient needs to start Remdesivir at the time of enrollment. We suspect that most will be using it as standard of care, but would like to have it declared at the time of enrollment.
- Lisa LaVange: What's the relationship between ACTIV-2 and ACTIV-3. Are we testing the same drugs? Are we enabling some learnings from one trial to the other with some kind of formally designed Bayesian design? For ACTIV-2, we've been trying to develop Bayesian rules to predict transition from Phase II to Phase III – haven't thought much in the inpatient setting. Of course we can't do everything at once – it takes a lot of work to build the simulation model – but we would want to be smart.
 - Jens Lundgren: Judy Currier is on the protocol team to provide input from the ACTIV-2 perspective. In terms of setting up the DSMB, would that be separate or the same to

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maintain continuity to learn across the trials. We haven't had a formal decision on how to set that up.

- Judy Currier: NIAIDSDSMB would probably be the same DSMB for these trials. At the summit we will learn which companies will participate. We would need to set that up to share information cross studies.
- Jens Lundgren: It would be critical for safety data at early part of the study as we expect sparse information coming in. We've also thought about how to enroll patients in Stage 1 to get an adequate safety signal
- Jens Lundgren: We are working towards Bayesian rules for moving from Stage 1 to Stage 2. Karen Price from ACTIV-2 team has been involved to help develop language around that.
 - Joe Koopmeiners: I will be having a discussion with Karen Price later on simulation model to understand the operational characteristics.
- Michael Hughes: Is virology in any part of the study?
 - Jens Lundgren: We've considered and deferred to not do it. The main rationale is that the dynamics for viral loads might not be reflective of antiviral efficacy.
 - Michael Hughes: Fair point. Really, safety information would be the most value to be shared across studies.
 - Jens Lundgren: If you find an efficacy signal, you may be moving your trial quicker than ours, or vice versa. That may or may not be relevant for the other trial - that level of discussion may be relevant
- Michael Hughes: Is your study going to be out-enrolled against our study that get hospitalized?
 - Jens Lundgren: The exclusion criteria for ACTIV-3 is the patient cannot have infusions of mAb prior to enrollment because bases on the kinetics studies, they would stay in the body for 2-3 weeks.
 - Michael Hughes: What about placebo recipients from our study?
 - Jens Lundgren: We should carefully discuss that. If a placebo patient gets unblinded from ACTIV-2, should we allow them in to ACTIV-3?
 - Michael Hughes: It's an important discussion because they would be done at the same site.
 - Ab Babiker: ACTIV-2 might not allow that.
 - Jim Neaton: It seems to be more of an issue for ACTIV-2 to unblind someone in the middle of the trial. Co-enroll once they advance
 - Samuel Brown: Are there key secondary endpoints from ACTIV-2 measured after hospitalization?
 - Judy Currier: 90 days is the last endpoint.
 - Jens Lundgren: That data from is taken from ACTT-1 - 40-50-% recovered by Day 28. Mortality and intensity might not have unfolded by Day 28.

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- Taylor Thompson: Day 28 mortality is 20%. Day 60 mortality is 28%. Day 90 mortality is around 31%. After Day 90 mortality rate plateaus.
- Paul Klekotka: Question about the ordinal scale as primary endpoint – it has lots of end-organ dysfunction rather than COVID-specific things as in other protocols.
 - Jens Lundgren: This is a topic we discussed earlier today, and decision is pending. The gist is that although COVID is a pulmonary disease, hypoxemia is an important aspect of the disease. The evolving understanding is that there are other features throughout the disease that contribute to morbidity and mortality. If there are other complexities, they should be included.
 - Jim Neaton: To clarify, this is not the primary endpoint. Primary endpoint is time to recovery. The ordinal outcomes are for early decision for enrollment expansion, proceeding to Stage 2, etc.

Next Steps

- Stacey Adam: For ACTIV-2, targeting first patient in early July. This might be mid-July
- Stacey Adam: With respect to the mAb summit – we are getting a good response from companies (started with 7, now up to 9-10). It should be a productive discussion. We are asking the master protocol leads to do a quick presentation on the snapshots of the trials and snapshots of key decisions and why they are made to (pre-empt questions from the group). We will be sending pre-read out to the companies. We will solicit feedback from the companies, and these will be shared with the protocol leads. Thank you for getting these synopses done – overall coming together and we are in good shape
 - Jens Lundgren: When are the documents getting out?
 - Stacey Adam: They are going to go out in 15 minutes. We are providing the context that all documents shared are in draft form, encouraging them to provide feedback.

Chatbox

From Lisa LaVange to Everyone: 12:10 PM

A reason to view randomization as two steps is to allow other drugs to enter later, and also to allow for a patient to be excluded from one drug but not others due to a drug-specific exclusion criterion.

From Samuel Brown to Everyone: 12:24 PM

Agreed. Pooling shared placebo seems easy under that assumption as well.

From Birgit Grund to Everyone: 12:34 PM

The setup proposed for ACTIV-3 is equivalent to a 2-step randomization, the randomization is to a drug-specific placebo (whether or not the "drug-specific placebo" is actually physically different).

From Wesley Self (Vanderbilt) to Everyone: 12:47 PM

Thursday, June 4th, 2020

Will definitions of each level of the ordinal scale be finalized by the group on early morning (US time) calls?

Tuesday, June 2nd, 2020

Action Items

Action Items		
	Information	POC
1	Share with the INSIGHT team the list of operational items (without comments) from Laura McNay as a starting point to map out operational capabilities	Stacey Adam / Jens Lundgren / Jim Neaton
2	Share list of operational needs with CTSN, PETAL, and VA to identify opportunities for cross-network collaboration	Stacey Adam

Notes

Agenda Overview

- New members joining: Representatives from NHLBI/CTSN, NHLBI/PETAL, VA, and Clinical Trial Capacity Working Group
- Review synopsis of ACTIV-3 master protocol (drafted over the last weekend) to turn over to the companies for the mAb summit
 - Draft by this Friday
 - Outline to be reviewed in mAb Steering Committee
- Operations discussion: specific protocol needs, coordination with ACTIV-2, preferred CROs alignment

Master Protocol Updates [Refer to Jens' Presentation]

- ACTIV-3 is short-titled 'TICO' – open to other suggestions
- Slide 2: Condensed hypothesis
- Slide 3: Specifics still under discussion
 - Stage I aimed at identifying activity (i.e., drugs to move forward to Phase II)
 - Stage II aimed at efficacy; note effect size should be 25% increase in time (not 30%)
- Slide 4: Ordinal outcomes to focus on; been validated in ACTT-1 to capture clinical benefit
- Slide 5: Based on data received from ACTT-1
- PI of this study would be Jim Neaton from University of Minnesota
- The version Jens presented reflects discussion from the Writing Team meeting yesterday and is continuing to evolve based on discussion with the Stats Team and the Writing Team this week
- With respect to the odds ratio: Statisticians provided feedback that we shouldn't control for Type 1 error for multipin agents. We've reduced the Type 1 error, eliminated Bonferroni correction, and reduced odds ratio from 1.35 to 1.25 for recovery.
 - This is more conservative compared to the 85% power the ACTT group is using

Tuesday, June 2nd, 2020

Operations Discussion

- Laura McNay shared a document outlining operational items that (b) (4) has competency to cover provides an overview. Discussion between DAIDS and (b) (4) has started to identify what items to be covered by which organization. Interested to align with this group on how to coordinate across networks and agencies to handle operations
 - ACTIV plays a facilitative role. The networks will be leading the logistics operations
- Jim Neaton on INSIGHT existing capabilities and outstanding needs
 - Existing capabilities:
 - Specimen collection, transport, and storage (worked with a central repository)
 - Data collection
 - Drug distribution (worked with a company with depot for drugs that can ship to sites in EU, UK, US, and South America)
 - Outstanding needs:
 - Resources to collect protocol registration documents from sites
 - Site monitoring
- Vicky Davey: No red flag from VA. Can check to see if there are any CROs that VA has worked with for site registration
- For site monitoring, would be important to consider remote monitoring capability as traveling is limited at the moment
- It would be good to coordinate with the same contractor for multiple networks to keep it simple and maintain uniformity and data integrity
- CTSN is happy to partner on site registration and monitoring.
- CTSN also has sites in US, Canada, and Germany – are you interested in partnering with the network and sites in other countries?
 - German sites will operate through Jens' ICC. There may be some overlap between the networks to be worked out offline.
- Taylor Thompson: PETAL is flexible and happy to collaborate. Can help with regulatory documents, setting up payment for the sites, etc. The need for site monitoring for a registered trial like this might exceed PETAL's capability
 - INSIGHT has established a payment structure with its site
 - Would need to establish a central IRB, potentially through the established process by CTSN / PETAL
- With respect to clinical data management and clinical reporting, currently the plan is to do that at University of Minnesota working with collaborators who have experience in this topic.

ACTIV, Therapeutics-Clinical Master Protocol Subgroup,
ACTIV-3 Operations Team, Key Takeaways

Tuesday, June 2nd, 2020

- *Should that be coordinated with ACTIV-2?* Inpatient and outpatient would be different reporting structures. Can leverage INSIGHT-13 and get that rolled out quickly
- *Is it done separately for ACTIV-2 and ACTIV-3?* Don't know what ACTG is doing. Know it's going to be through (b) (4) – that's not our plan and it might slow us down. Worth a discussion with ACTG

Recap and Next Steps

- Start with INSIGHT to collect existing mechanisms / capabilities to conduct operational efforts
- Distribute to the broader group how the capabilities can be supplemented and / or expanded
- Discuss the path forward for remaining gaps as a group (i.e., contract CROs, engage (b) (4), etc.)

Chatbox

ACTIV, Therapeutics-Clinical, mAb Steering Committee

Key Takeaways

Friday, May 29th, 2020

Action Items

Action Items		
	Information	POC
1	Share the document outlining the safety data requirements prior to entering Phase II of ACTIV-2	Peter Stein / John Farley
2	Establish a trial oversight committee for the ACTIV trials and develop a charter to document the decision-making process	Stacey Adam / Janet Woodcock
3	Share ACTIV-2 and ACTIV-3 synopses with the mAb Steering Committee once available	Stacey Adam
4	Let Stacey Adam know if you would like to stay on as part of the Trial Oversight Committee for ACTIV-2 and/or ACTIV-3	mAb Steering Committee

Notes

Opening

- ACTIV-2 master protocol will go into FDA review next week

mAb Clinical Summit

- Date and Time: 12pm – 2pm ET on June 9
- Working through logistics
- Kevin Bugin is working on company outreach, soliciting basic information about the mAbs and high-level timeline for development. May give this group an estimate of number of mAbs even before the Summit
- Been talking with DCR/DAIDS to supplement networks. If needed, Kevin's group can issue an RFP for additional vendors
- Protocol synopses available for internal review by end of this weekend. Need to decide whether we submit two synopses or synopsis for ACTIV-3 and full protocol for ACTIV-2
- Have requested questions from Judy Currier and Jens Lundberg for the company – need them by mid next week to be included in the pre-read
- Peter Stein is happy to participate. OWS would prefer to have representation from active FDA members for regulatory presence and input

mAb Sub Team Updates

- Panel of mAb experts from NIAID and companies who are developing mAb has been working on defining a set of minimum entry criteria
- Presented at the full working group and received feedback that the criteria are not 'minimal' enough. Team is working on amendments to simplify. Aim to complete next week

ACTIV, Therapeutics-Clinical, mAb Steering Committee

Key Takeaways

Friday, May 29th, 2020

- Would be helpful to clarify that these are the minimum criteria for Phase II entry – need to re-iterate with the team about that point
- Lisa LaVange: Are we allowing agents to come into either Phase II or Phase III?
 - To be discussed later in the meeting but leaning towards having agents enter through Phase II to avoid losing learning
 - Peter Klein: We need to specify two sets of criteria – for entering Phase II and for entering Phase III
 - Stacey Adam: For the latter it would be mostly collected from Phase II. The mAb panel is focused on defining criteria for entering Phase II
 - Additional support for really good candidate mAb with solid Phase II data to scale?
 - There is a working group in the government focused on that issue to identify key with mapping and modeling
 - Would like to know what the clinical indicators are to ensure that we are collecting that information
- Minimum entry criteria
 - Tox, cross-activity, etc. would've been reviewed prior to Phase II
 - Stacey Adam: Based on John Farley's comment, the requirement is completion of a single ascending dose study for large safety worries in any population. The toxicology bar would depend on the population
 - Hospital: PK and initial tox in relevant species
 - Ambulatory: tissue cross-reactivity, start of reverse GLP tox in relevant species
 - Healthy volunteers: reverse GLP tox in relevant species needs to be completed in large population
 - **Peter Stein and John Farley have a documented for specific requirements that they can share**
 - Important to understand what the FDA requirements would be if companies did Phase I elsewhere
 - Lynn Marks: Instinct is that single agents are going to have escape mutants – it's about how we handle them (i.e., progress or include in combination, etc.)

ACTIV-2 Update

- Protocol went through the CSRC review on Thursday and got some good feedback
- Additional Bayesian language for the stats section are added
- Will be reviewed by FDA next week
- Updated synopsis over the weekend

Friday, May 29th, 2020

- Question around entry directly into Phase III - Prefer not to because we'd lose learning. If they have comparable Phase II data (i.e., virology and symptoms), then there should be a mechanism for the Steering Committee to review and make a decision. We need to identify the mechanism for making those decisions and document the process
 - Likely the mAbs are in early stages of development. Companies may decide to do Phase II on their own
 - Need to charter the Steering Committee to make these decisions – wouldn't be part of the master protocol but a super structure over the protocol
 - By allowing direct entry into Phase III direct entry, we lose the statistical power and we are uncoupling Phase II and Phase III of the master protocol and become less seamless
 - Can make it operationally hard to enter Phase III directly but with a strong candidate with comparable Phase II data we should include it
 - One option is to allow an agent into Phase III operationally (i.e., seamless Phase II/III with a Phase III "add-on")
- Bayesian framework can be implemented before the first agent without prior knowledge to apply
- Lynn Marks: Can I get government funding outside of this master protocol? Or is all government fund being channeled through this master protocol?
 - Janet Woodcock: We are making progress to coordinate all concurrent efforts
- Joan Butters: If a molecule is selected into ACTIV-2, how many touchpoints does the agency expect the company have throughout the process?
 - Peter Stein: Safety reporting requirements would have to be met - that would be the largest portion for this seamless Phase II/III trial
- Libby Higgs: Would it be acceptable to bring in a small molecule alone or in combination with an mAb into the protocol? If so, what is the route?
 - Janet Woodcock: Having an overall Steering Committee (not specific to mAb) can decide sub studies, i.e., with small molecules. For example, oral would be a different sub study because it involves a different placebo. I think it's possible.
 - Lisa LaVange: Issue with limitation with sites? Do we keep adding to this protocol or running multiple master protocols?
 - Trial oversight would help to council which would be the more efficient route
 - Janet Woodcock: We plan to augment the sites with bandwidth and capacity
 - Peter Stein: With small molecule you would need different monitoring and it would be a small molecule protocol. Can use the same framework as ACTIV-2 as a basis
 - Lynn Marks: Anticipation is good quality small molecules would be few and far in-between
 - Wave 2 prioritization for immunomodulators, antivirals, and symptomatic / supportive candidates will be starting up soon. RFI survey to collect data on candidate agents will be

Friday, May 29th, 2020

launched by end of today (over the weekend the latest). We will then get together to adjudicate for the next round

- Joan Butters: Should aim to have small molecule master protocols set up soon to maintain connection with the ACTIV initiative
- Peter Stein: Regarding timeline for DSMB review, we can facilitate our review. Would take some time from clinical and OT to review. Would be helpful to know when that would be submitted.
 - Pre-IND submission expected from MaryAnne Luzar (from NIAID) on Monday next week

ACTIV-3 Update

- Jens Lundgren would be the PI of the ACTIV-3 master protocol. One of the leads of the INSIGHT network (the other is Jim Neaton)
- Started development recently
- Synopsis of ACTIV-3 will be developed over the weekend
- Lisa LaVange: Would this have more in common with ACTIV-2 (being mAb) or with ACTIV-1 (being inpatient)? Would you be doing this in parallel with Lilly's agent?
 - Jens Lundgren: Currently looking at ACTIV-1 as a basis. INSIGHT has been supporting ACTIV-1. Parallel protocol, INSIGHT 13, is an aspiring document for developing the synopsis
 - Deadline for protocol to be written - Synopsis by Monday and draft protocol by Friday
 - Janet Woodcock: I would assume inpatient and outpatient studies would run concurrently
 - Judy Currier: inpatient mAb is a lot like ACTIV-1 but ACTIV-1 involves repurposed drugs so we know more about the safety. Key is what's the gating in an inpatient setting
 - Jens Lundgren: We would have a smaller Phase II and have "stop-go" criteria to quickly ramp up to Phase III
 - Peter Klein: If you are seeing a good dose in outpatient Phase II, do you take that dose to inpatient Phase III? We might need to push to the next dose level in an inpatient setting.
 - Carl Garner: We'd like to do it in parallel. We don't know what to expect as virology is down – you might need more dose. We don't have any correlation at the moment
 - Jens Lundgren: Current thinking is to allow two or three doses for Phase III of ACTIV-3
 - Sam Bozzette: Would you also allow direct entry Phase III? Yes
 - Carl Garner: In an inpatient setting, decision making is more straight-forward than outpatient. We are looking at two doses in outpatient. We would stay with 1-2 doses with inpatient
 - What would be the Phase II endpoint? 6 different options at the moment - team is working to condense
 - Endpoints for inpatient wouldn't translate with outpatients

ACTIV, Therapeutics-Clinical, mAb Steering Committee

Key Takeaways

Friday, May 29th, 2020

- Joint meeting between mAb Steering Committee and ACTIV-3 Writing Team next Friday – aim to review an initial draft

Action Items Update

- #1: Complete
- #2: Does not have enough data – will share with more data. There is some recruitment issue

Outstanding Question for the mAb

- Would this group be interested in staying on as part of the Trial Oversight Committee for ACTIV-2 and/or ACTIV-3? Please let Stacey know as soon as possible.

Chatbox

From (b) (6) to Everyone: 02:10 PM

I vote synopsis for both - that way 2 & 3 look similar and having only the synopsis will help keep people out of the weeds

From Libby Higgs to Everyone: 02:10 PM

Sam, Agree.

From (b) (6) to Everyone: 02:43 PM

agree with Peter

From (b) (6) to Everyone: 02:53 PM

Aligning with 1 more than 2 seems to make sense because of the patients status

ACTIV, Therapeutics-Clinical Master Protocol Subgroup,
ACTIV-2 Writing Team, Meeting Minutes

Thursday, May 28th, 2020

Action Items

Action Items		
	Information	POC
1	Follow up with the OWS team and inform this group: For learning purposes, do we allow entry into ACTIV-2 Phase II if there might be logistics / manufacturing issues to proceed through Phase III?	Stacey Adam
2	Raise the question with the mAb Steering Committee on whether agents can enter directly into Phase III portion of the ACTIV-2 master protocol	Stacey Adam / Judy Currier
3	Share the roster of the mAb Steering Committee members with this group	Stacey Adam / Helen Chen
4	Initiate the conversation with the mAb Steering Committee to gauge interest for the group to stay onboard past the initial guidance phase to oversee the ongoing operations of the mAb trials	Stacey Adam
5	Follow up with (b) (6) and/or (b) (6) from (b) (4) on questions from CSRC	Davey Smith
6	Share with Stacey Adam the updated version of the ACTIV-2 master protocol and protocol synopsis by end of week, which Stacey will distribute to OWS and this team	Laura Hosey / Stacey Adam
7	Circle back with Judy Currier on the meeting cadence for this team for next week	Stacey Adam
8	Draft the master protocol appendix for the Bayesian framework	Karen Price/ Michael Hughes

Notes

Opening

- Judy Currier: The inpatient study is also planning to do a Phase II and a Phase III. Some companies plan to do Phase II in inpatient setting and transition to outpatient. How do the two trials complement each other?
 - Stacey Adam: That's what INSIGHT is thinking as well. We can potentially harmonize from the design perspective. Clearly endpoints would be different for the two trials. For companies who are earlier in development, they might want to do exploratory dose studies in an inpatient setting before outpatient. The companies may want to go into one study before the other or go into both at the same time. We will know more after going through the summit.
- Judy Currier: In addition to the agenda topics, Joe and Davey have a list of issues we need to resolve but we can start with the agenda.

Updates

- mAb Steering Committee Updates
 - Stacey Adam: We have received guidance from FDA during the mAb Steering Committee Meeting – write up for that meeting will be available some time today. An agent needs to

Thursday, May 28th, 2020

have a dose study done prior to entering Phase II but not necessarily with us. We can potentially provide additional support to get that done.

- Stacey Adam: The Steering Committee also discussed whether we want to allow company to directly go into Phase III – we may lose learning but for some companies, there are efficiency benefits.
 - Judy Currier: If they do Phase II in an inpatient setting, how do we integrate that to the outpatient protocol for Phase III?
 - John Farley: We are thinking the safety data would be relevant. Not sure if we will have comparable inpatient Phase II data to support outpatient Phase III, but the safety data would be relevant to support the expansion of the study.
- ACTIV-2 Stats Team Updates
 - Michael Hughes: I am working with Karen to write the appendix section for the Lilly agent, which would bring in the Bayesian framework. If the team is amendable to change the graduation rules at the end of Phase II to be more in the flavor of probabilistic statements, we would be good to develop that further. My preference is to leave the Phase III in a standard frequentist framework – would be an easier way to go with multiple agents and international implications.
 - Karen Price: That's a reasonable way to progress to incorporate the learning paradigm. We discussed a couple of key things during the Stats Meeting:
 - We reviewed some simulation results. There is more work to do around Bayesian success factors incorporation.
 - One question we had is around jumping to Phase III for some compounds. We lose learning from virologic endpoints and understanding of symptoms across agents in order to develop a model to predict probability of success for Phase III. We continue to push towards an inferential learning paradigm, but we need to be careful with how we do testing and acknowledge what we lose.
 - We discussed the consent process and how we randomize patients.
 - Judy Currier: Would we allow molecules to come into Phase II that has uncertainty to proceed to Phase III (e.g., logistics issues) for learning purposes?
 - Stacey Adam: OWS might be able to assist us on this as they also help solve logistics and manufacturing. We would need a conversation with that team to see if we have the ability to assist.
 - Dionne Price: Is ACTIV hoping to sponsor a prevention protocol? Phase II data for that group would support that.
 - Sarah Read: There are lots of effort for prevention going on within NIAID. It has not been a focus for ACTIV. For now, we would leave that to NIAID to proceed and can pull in relevant stakeholders to align.
 - Judy Currier: It would be good to coordinate that to collect additional data.
 - Dionne Price: Is the goal to be inferentially seamless? Are they meant to be distinct portions?
 - Michael Hughes: Inference is pretty straightforward. We can look at data at the endpoints and interims of Phase II. Impact on design would be minimal – the type of stopping rules (i.e., efficacy) makes it hard to stop early in the study. That's one way to deal it.

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- Karen Price: It's fairly easy to get through those gates (i.e., based on symptoms and virology presently). We are building a model to relate these end points to Phase III endpoints (i.e., hospitalization and death). With the current protocol, when time comes, we are making inference on hospitalization events across interims of the trial.

Davey's List of Topics

- Davey Smith: Will we standardize graduating rules from Phase II to Phase III?
 - Judy Currier: It will evolve over time. Need to set some rules up ahead of time and play by them. We need to nail down how that would work.
 - Sarah Read: I wouldn't be comfortable to set the rules right now. Maybe we set up a minimum standards at the moment and adjust as we learn more.
 - Karen Price: Appendix can contain probabilistic statements -probability in difference % patient who clear at any time in time – if that probability exceeds 70%, they would meet the graduation criteria. Similar to that on symptoms, it is based on % improvement in time to resolution. The committee would get what the probabilities are and what was met, in theory it should be algorithmic.
- Davey Smith: How many agents can we run in the trial? There may be a capacity issue depending on study size and enrollment. Should the committee decide on that?
 - Judy Currier: There is no issue from the design perspective. This is more of an operations decision about capacity – how do we decide how many sites we need.
 - Michael Hughes: Conceptually that's correct. Devil is in the details on sites, etc. Everything going into Phase III would require 1000 participants. Then it's a scale and rate of accrue issue. The more agents we include the longer it would take since we are sharing participants.
 - Davey Smith: Good. I just want to be on the same page as there's a question around whether there is there a max of agents we are limiting.
- Davey Smith: How do you decide whether the agent becomes standard of care?
 - Judy Currier: One way is to go by recommendations of the guideline groups – they set the standard for the field.

Joe's List of Topics

- Davey Smith: Can agents enter directly to Phase III? The agreement is that that they can. We would need to define formalized criteria for entry.
 - Judy Currier: It's not ideal. We would need to get a decision from the Steering Committee.
 - Stacey Adam: I would suggest a proposed solution for the Steering Committee to evaluate. We would also want to limit how many we are allowing to come in.
- Davey Smith: How many doses per agent for the dose-finding run-in? Do we have any dose finding before Phase II?
 - Judy Currier: It has been decided that an ascending dose study is required prior to Phase II. The dose study is not part of this study but could be facilitated by ACTIV if needed.
 - Stacey Adam: Comment from the FDA suggests that two doses would be fine.
 - Sarah Read: We say yes unless someone objects.

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- Karen Price: In the protocol, how is that flexibility of allowing two doses documented? Is it treated as a separate agent? Once the patient is randomized to the agent, then they are randomized to a dose?
- Davey Smith: I'm thinking we treat it as a separate agent but there are reasons to do it differently. It's cleaner this way. From a virologic standpoint, there are good reasons to treat them separately. It is riskier to do a lower dose – it might be bimodal and not a continuum.
- Judy Currier: We want each arm to be the same size with multiple doses on this?
- Karen Price: Having full arms is fine. This could be the default unless there's scientific rationale to do it differently.
- Davey Smith: Does the placebo ever expire?
 - Sarah Read: I thought we said we would want to have concurrent controls?
 - Judy Currier: Is there a way to examine if the outcome of placebo changes over time? If it doesn't, then we don't need to exclude placebo.
 - Michael Proschan: If the agent changes over time, then we only use the placebo after the agent starts.
 - Judy Currier: Essentially, we will always use concurrent controls.
- Davey Smith: We agreed to make the protocol to be the "barebone" and applicable to all drugs, and any additional evaluation would be in the appendix?
 - Judy Currier: Right. Confirmed.
 - Davey Smith: We might not need all blood draws / NP swabs for everything. If you have an agent that you know are not getting therapeutic effect until 14 days, you might not need Day 3? I think we need to keep all NP swabs.
 - Judy Currier: I think you need some minimum. We would only take out some blood draws in Phase III.
 - Paul Klekotka: Phase II would be similar across arms. You don't want to make them so different so you have differential dropouts, otherwise we would lose the ability to compare to placebo.
- Judy Currier: Through ACTG we have a network of virology support labs to help standardize assays, etc. John Li has met with the virologists. They are developing a quantitative assay that would be feasible and standardized. We will have very nice virology support through NIAID and the network to have a consistent plan for virology. Those methods would be described in more details in the protocol.
- Judy Currier: It might be helpful to get names of the active mAb Steering Committee to have clarity on who the decision makers are.
 - Stacey Adam: We can have the conversation with the mAb Steering Committee to confirm the duration of engaging with that group. Some members might not be able to stay on long term to oversee the trial operation. We can ask them - maybe a subset of the group can oversee both mAb trials, or half of them can oversee one while the other half can oversee the other.
 - Stacey Adam: There is also a request around whether ACTIV will continue to oversee some of these master protocols, and / or whether additional governance needs to be established. We will get more clarity. There might be a role for us in that.
 - Sarah Read: Similarly, will OWS need to oversee these protocols, whether independently from ACTIV or through ACTIV?

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- Stacey Adam: Suspicion is through ACTIV.
- Judy Currier: We have confirmed agreement from (b) (4) to move forward. More agents to come from the agent prioritization effort. We will continue forward with (b) (4)'s asset as we are eager to finalize protocol and move it in the field.
 - Davey Smith: I need to follow up with (b) (4) on some questions from the CSRC meeting as well as getting some of their Phase I data from Phase I, some questions from CSRC.
 - Paul Klekotka: Let me and Ajay know. We got a list from Kelly that we are going through.
 - Judy Currier: CDA is already in place through NIAID.
- Michael Hughes: Janet is taking a version of the protocol to the companies? What version is that?
 - Stacey Adam: The version by this weekend. Inpatient trial is going in with synopsis. I would recommend submitting something similar for easy comparison
 - Judy Currier: They should see the final version of the protocol. This would help eliminate some questions and uncertainties around when the protocol will be in place. Laura Hosey or Joanna could send the latest.
 - Stacey Adam: Share with me the version that you are comfortable to have the companies review, along with any caveats. Janet has been referring to synopses so would be helpful to update the synopsis.

Summit Update

- Team met with OWS to gain more clarity on the summit. ACTIV is playing more of a lead role to set up the summit. They request finalized synopses by tomorrow, if possible, or by the end of this weekend. Team will do a quick internal review and have them forwarded to the companies by Tuesday. We are aiming to hold the Summit on June 9 (or that week). Coming out of that summit, we would like to achieve the following:
 - Understand who wants to participate. For participants, are there any apprehension
 - Timelines for development of where they are
 - General needs and knowledge
- The summit is going to be smaller than anticipated. We are inviting the original 9 companies and some additional ones. The focus is on ones that are potentially ready this year and we will engage with other ones later. We are looking in the realm of 6-7 that would come forward this year.
 - Peter Kim: This year means calendar year? Yes. 2020
- John Farley: As soon as you have a protocol you should submit that to the FDA for pre-IND review. IND review would be very quick but pre-IND would take a while.
 - Cyrus Javan: That is the plan. We are aiming to submit early next week.
 - Stacey Adam: We are planning to invite John Farley to the summit to listen in and weigh in from regulatory perspective. We will also send John Farley and Peter Stein the synopses. Janet is not fully aware of FDA's continuous involvement during the development of these master protocols and want FDA input on these.
 - Peter Kim: John, should we copy you when we send in pre-IND? You can but I'll know it's there.

Chatbox – N/A

High-Level Meeting Summary

The Monoclonal Antibody (mAb) Writing Team of the ACTIV Therapeutics-Clinical Working Group (TX-Clinical WG) briefed the mAb Steering Committee (SC) on the status of the outpatient mAb (ACTIV-2) master protocol. The Writing Team requested SC input on trial design, in particular addressing the need to define the minimum data for entry into ACTIV-2. The Writing Team and SC also discussed refinement of Phase II endpoint analyses; progression of candidate agents to Phase III, including criteria for direct Phase III entry; and strategic flexibility of the ACTIV-2 master protocol. Finally, TX-Clinical WG Co-Chairs provided a brief update on the INSIGHT network for mAb inpatient trials.

A summary of key discussion points follows.

ACTIV-2 Master Protocol Update

To rapidly and efficiently evaluate multiple potential therapeutics for COVID-19 in an outpatient setting, the ACTIV-2 master protocol proposes an adaptive platform trial with a seamless Phase II/ III design that permits staggered enrollment of candidate agents. Dr. David (Davey) Smith briefly reviewed the proposed ACTIV-2 protocol, highlighting key design parameters:

- **Agent selection** – prioritization based on activity against SARS-CoV-2 entry or replication, Phase I pharmacokinetic and safety data, and potential to expand to Phase III if effective.
- **Eligibility criteria** – ambulatory adult with active SARS-CoV-2 infection within 7 days prior to entry and at least one symptom of COVID-19; not participating in another COVID-19 trial.
- **Stratification** – based on risk (e.g., over 50 years of age and/or co-morbidities such as diabetes, hypertension, cardiovascular disease, obesity, lung disease) and duration of symptoms at time of study entry.
- **Randomization scheme** – patients randomized first to candidate agents and then to agent versus placebo.
- **Phase II endpoints** – symptomatic and virologic endpoints; primary endpoints are duration of COVID-19-associated symptoms and proportion of negative nasopharyngeal (NP) swabs for SARS-CoV-2 RNA (at days 3, 7, 14, 21, and 28). Secondary endpoints include ranked symptom severity scores, self-reported return to health, and viral load (defined by area under the curve [AUC] analysis) correlated to daily self-collected nasal swabs.
- **Study visits** – during Phase II, blood draws and NP swabs at specified timepoints over 28 days; during Phase III, blood draws only at specified timepoints over 28 days.
- **Phase II decision** – graduation (i.e., agent reaches primary symptom or virologic endpoints) or termination (based on evidence of resistance or safety issues); decision by Trial Steering Committee, composed of members of NIAID, ACTIV, and study team.
- **Phase II analysis** – powered to detect 20% reduction in symptom and virologic endpoints.
- **Phase III endpoints** – death (any cause) or hospitalization within 28 days post-study entry; Phase III includes built-in interim analyses at 25%, 50%, and 75% timepoints, allowing for rapid termination of candidate agents that do not show efficacy.

Considerations for ACTIV-2 Trial Design

The mAb Writing Team and SC reviewed specific design elements of the Phase II and Phase III studies under the proposed ACTIV-2 master protocol:

Minimum Requirements for Entry to ACTIV-2

Members of the Writing Team emphasized the need to clearly define and articulate minimum data necessary for agents to enter ACTIV-2. They agreed that all candidate mAbs should have preclinical toxicology data, as well as Phase I safety data and single ascending dose studies in any population to confirm safety and pharmacokinetics. However, participants debated whether dose ranging studies should be required before candidate agents enter ACTIV-2.

The current ACTIV-2 protocol allows only two doses for each candidate agent in Phase II, precluding the possibility of dose ranging studies. However, in a recent meeting with mAb developers, the mAb Subteam found that almost half felt they needed additional dose finding before moving into Phase II studies. The Phase II component of ACTIV-2 could theoretically accommodate the visits and monitoring necessary for dose ranging studies. However, doing so would require expanding the number of doses allowed under the master protocol. SC members recognized that this expansion could strain ACTIV-2 resources. ACTIV-2 would also have to address several additional considerations, including the uncertainty of sample sizes necessary to model pharmacodynamics with virologic endpoints for COVID-19 and the pragmatic challenges associated with increasing the ACTIV-2 scope to include a Phase I component.

ACTIV-2 would also need to meet the FDA minimum bar for data to enter Phase II, which were relayed by Dr. John Farley at the FDA. Dr. Farley shared FDA's perspective on the minimal amount of data a company would need for this study. The FDA relayed that they would require at least a single ascending dose studies for major safety issues, which can be done in any population (outpatient or inpatient). They indicated that the dose finding population would likely depend on toxicology data available by first in human (FHI) studies. For hospitalized patients, FDA has extended regulatory flexibility, so in this population only PK and initial toxicology data in a relevant species. For ambulatory, the FDA would want to additionally see tissue cross-reactivity data and the reverse dose GLP toxicology started. For healthy volunteers, the FDA would wish to see the reverse dose GLP toxicology completed. The FDA is also allowing companies to move from single ascending dose finding to dose ranging studies in ambulatory ill with 3-4 arms of 40-50 patients per arm. This type of study would allow the company to enter two drugs into ACTIV-2.

For these reasons, the SC believed that dose ranging studies should be completed prior to ACTIV-2 entry. Dr. Janet Woodcock suggested that other teams (e.g., Operation Warp Speed) could potentially resource dose finding studies for candidate agents, which would preserve the current scope of the ACTIV-2 master protocol.

At the same time, the SC concluded that ACTIV-2 must meet the needs of mAb developers to be successful. They recommended reaching out to these companies for input on ACTIV-2 trial design and to define the need for potential external support to complete dose ranging studies

prior to ACTIV-2 entry. Dr. Janet Woodcock noted that Dr. Francis Collins is planning a second clinical summit. She agreed to facilitate communication with the attending companies, requesting feedback on the ability of ACTIV-2, as currently designed, to meet their needs.

Refinements to Phase II Endpoint Analyses

To determine viral load via nasal swab, the ACTIV-2 protocol proposes AUC analysis using quantitative PCR (qPCR). However, because the qPCR analysis is not yet optimized, viral load is not a primary endpoint for Phase II. The team plans to optimize the qPCR analysis for viral load using exploratory data generated from Phase II studies.

Some members favored the inclusion of a *time-to-event analysis* for phase II virologic endpoints. However, the limited granularity of viral assessments using NP swabs (with only 5 during the 28-day study period) precluded this type of analysis in the proposed ACTIV-2 protocol. To address this challenge, participants suggested using the self-administered nasal swabs, which are collected daily, to increase viral assessments for time-to-event analyses.

Progression to Phase III Studies

Phase II evaluation of candidate agents will result in graduation to Phase III confirmatory studies or termination. It is possible to extend Phase II for agents that show an effect but are not deemed ready to graduate to Phase III. However, it is unclear whether additional data collection for extended Phase II agents should be collected as Phase II or Phase III data.

Graduation or termination of candidate agents depend on both person-based (i.e., SC) and rule-based (i.e., symptomatic and/or virologic endpoints) inputs. While SC input is vital (e.g., to resolve ambiguity in data or identify underlying reasons for poor virologic endpoint performance), participants agreed the protocol would benefit from increasing rule-based inputs by incorporating Bayesian analysis. They recommended that statisticians adjust for Bayesian decision making at the end of Phase II of the ACTIV-2 study. Dr. Karen Price will discuss the proposed Bayesian approach in more detail during the statistics meeting on May 28.

Direct Entry of Candidate Agents to Phase III

The Writing Team and SC discussed whether ACTIV-2 should permit entry of candidate agents directly to Phase III of the ACTIV-2 study. The Writing Team generally favored allowing direct phase III entry for candidates with supporting data from an adequate external Phase II trial (i.e., one that generates comparable data to ACTIV-2), particularly given the urgent need to develop therapeutics against COVID-19. However, some members expressed two concerns about bypassing Phase II evaluation in ACTIV-2: (1) the loss of consistent data on the relationship between virology and symptoms across agents, which informs Phase II endpoints, and (2) the loss of factorial evaluation in Phase II of the study, which limits the ability to evaluate cocktail development. Dr. Woodcock noted that factorial design is not required for cocktails composed only of mAbs, provided that preclinical data shows the mAbs target different epitopes. However, factorial design is required for mAbs administered in combination with another class of drug (e.g., an antiviral agent).

Creating a Flexible Master Protocol

Members of the SC asked whether the frequency of blood sampling proposed during Phase III of the ACTIV-2 study was necessary. The Writing Team agreed that the number of blood collection timepoints for mAbs could be decreased to improve safety, while still maintaining sufficient sampling timepoints to evaluate the relationship of virology data with symptoms and hospitalizations and to inform Phase III activities.

The Writing Team's underlying strategy for blood sampling was to define the maximum allowable number of blood collection timepoints for Phase III in the ACTIV-2 master protocol, with reduced sampling for specific agents outlined in individual appendices. Members of the SC argued this strategy should be reversed, with the master protocol delineating the *minimum* number of blood collection timepoints with additional determinations included in the appendices, thus preserving flexibility in the master protocol. Dr. Woodcock emphasized that flexibility in the master protocol is critical for expansion studies. To complete anticipated target enrollment for Phase III studies, ACTIV-2 may need to recruit additional sites. Because these sites could vary in terms of sophistication and capabilities, a subgroup of study sites performing a more pragmatic trial (i.e., gathering only basic safety data and straightforward outcome measures) can improve both the power and speed of the overall study. Meanwhile, the research sub-study will continue to collect data at select sites. The Writing Team welcomed this recommendation but expressed minor concerns about how to write the master protocol and accompanying appendices to reflect this strategic change.

INSIGHT Update

ACTIV's goal is to harmonize the outpatient (ACTIV-2) and inpatient (ACTIV-3) mAb trials as much as possible. Dr. Stacey Adam anticipated receiving information and a synopsis from the INSIGHT network by end of the weekend May 31, 2020. She will forward this material to Dr. Woodcock.

Next Steps

Dr. Stacey Adam will provide a synopsis of the proposed ACTIV-2 Trial to Dr. Woodcock. Dr. Woodcock will then circulate this synopsis to mAb developers and request feedback on ACTIV-2 study design prior to the next NIH Clinical Summit.

Appendix A: Participants List

MEMBERS – WRITING TEAM

Kara Chew, MD, MS, *Infectious Disease Specialist, U. California, Los Angeles (UCLA)*
Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, UCLA*
Eric Daar, MD, *Chief, Division of HIV Medicine, UCLA*
Joseph Eron, MD, *Chief, Division of Infectious Diseases, U. North Carolina (UNC) School of Medicine*
William Fischer, MD, *Co-Director, Hemorrhagic Fever Research, UNC School of Medicine*
Lara A. Hosey, MA, CCRP, *Clinical Trials Specialist, AIDS Clinical Trials Group (ATCG) Network Coordinating Center*
Michael Hughes, PhD, *Director, Center for Biostatistics in AIDS, Harvard School of Public Health*
Arzhang Cyrus Javan, MD, MPH, DTM&H, *Clinical Representative, Division of AIDS, National Institute for Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)*
Jhoanna C. Roa, MD, *Clinical Trials Specialist, ATCG Network Coordinating Center*
David (Davey) Smith, MD, MAS, *Professor of Medicine, U. California, San Diego (ACTIV-2 Protocol Chair)*
David Wohl, MD, *Professor of Medicine, UNC School of Medicine*

MEMBERS – STEERING COMMITTEE

Samuel A. Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), NIH*
Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*
Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*
Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*
Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*
Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*
Karen L. Price, PhD, *Research Advisor, Eli Lilly and Adjunct Professor of Statistical Science, Baylor University*
Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*
Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

INVITED PARTICIPANTS

Kevin Bugin, MS, RAC, *Director for Special Programs, CDER, FDA*
Sylva Collins, PhD, *Director of Office of Biostatistics, CDER, FDA*
John Farley, MD, MPH, *Director of Office of Infectious Diseases, CDER, FDA*
Paul Klekotka, MD, PhD, *Sr. Medical Director of Immunology, Eli Lilly*

Marina Kozak, PhD, *Health Scientist, Biomedical Advanced Research and Development Authority (BARDA)*

Gilbert “Lynn” Marks, MD, *Senior Advisor to BARDA, Office of the Director*

Ajay Nirula, MD, *Vice President, Immunology, Eli Lilly*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Dionne Price, PhD, *Director, Division of Biometrics IV, CDER, FDA*

Michael Proschan, PhD, *Biostatistics Research Branch, NIAID, NIH*

Daniel Ruben, PhD, *Division of Biometrics IV, CDER, FDA*

Janet Woodcock, MD, *Director, Center for Drug Evaluation and Research (CDER), FDA*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

Kelly E. Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Sam Bozzette to Everyone 00:38:55

I would be in favor of allowing drugs that were evaluated in an adequate outside phase II trial directly into phase III of this study

Joseph Eron to Everyone 00:50:27

The issue is the virology is as yet not reliable and 40 or 50 patients per group may not give you the virology data for PD interpretation

John Farley to Everyone 00:53:33

The other thing to consider is cocktail development. The ACTIV Ph2 allows a look at combinations in a factorial way.

Carl Garner to Everyone 00:54:33

Agree. We need to be able to make arms available for cocktails which might be combinations from earlier arms.

Carl Garner to Everyone 00:54:48

And across sponsors if data support

Libby Higgs to Everyone 01:05:53

Exactly, we need to begin looking at mechanism for systematically generating preclinical data so we can look at combinations

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Action Items

Action Items		
	Information	POC
1	Draft emails to Peter Klein and John Farley to collect their feedback on including a Phase I run-in stage in the ACTIV-2 master protocol	Stacey Adam
2	Share with the ACTIV-2 Writing Team the updated protocol document with the latest simulation framework incorporated	Stacey Adam/Karen Price
3	Share with the ACTIV-2 Writing Team and mAb Steering Committee the set of slides Davey Smith prepared for the master protocol	Stacey Adam

Meeting Minutes

ACTIV-2 Trial Design

- Takeaway from the mAb subgroup meeting: taking an integrated approach to include an optional safety and dosing portion in the master protocol, i.e., an early 'run-in' Phase I.
- Judy Carrier: We would need guidance from the FDA on how many people we would need for the initial safety assessment.
- Ajay Nirula: The dialogue from the previous call seems to imply this would be first-in-human study which would bring in additional responsibilities. The 'run-in' would accommodate the different requests from different companies,
- Judy Carrier: One of the concepts is we can potentially have an outpatient (with COVID-19 and symptomatic but not hospitalized) brought into an inpatient setting for safety and dose information. Those people can potentially continue into Phase III for additional information. Need more clarification from regulatory colleagues
 - Ajay Nirula: That would be feasible in some settings. It would depend on the preclinical data available. There may be more comfort with traditional hospital setting
 - Judy Carrier: We would need more clarification from our regulatory colleagues – are these sick patients we are bringing into inpatient setting who are otherwise outpatients?
 - Joe Eron: I know our hospitals are doing everything we can not to have COVID patients who don't need to be in the hospital to be in their facility. Maybe CTRC-type of inpatient facility could accommodate COVID-positive people?
 - Judy Carrier: Could potentially use an unused hospital room for research studies. That might not be feasible for all hospitals.
 - Joe Eron: You would still need to staff the room. A nurse would have to be assigned to that bed for 24 hours. The hospitals might do it – we can convince them if the beds are not utilized. Patients would all need to be cohorted for enrollment and placed in a separate ward. Why would you not do it in healthy volunteers? Is it because it could have a different safety profile in sick people?

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- Davey Smith: Mostly ADE. As mAb decreases you are increasing the risk for ADE and if someone were to get infected. All the sites would have to do early Phase I study. We can potentially get super sites who would have the ability to do it as an outpatient/inpatient hybrid.
- Joe Eron: I'm not against inpatient but I'm concerned about having people with COVID who don't have to be hospitalized come into the hospital. Maybe there are centers who can do it, but we would have a hard time here.
- Eric Hughes: It would be hard to find those people.
- Eric Daar: It would be breaking ground for us at least. We might be able to do that in our GCRC equivalent but certainly not anywhere else.
- Judy Carrier: What's important would be how do we make it a run-in to this trial. It may need to be a completely separate protocol.
- Cyrus Javan: Rapid feedback from FDA colleagues would be helpful. I am also working with regulatory partners at DAIDS and can see where we can get some answers first
- Davey Smith: Should we have a separate Phase I study?
 - Stacey Adam: It's an option to have a small pilot Phase I study feeding into our study. My assumption is that the regulators would be receptive, but it would pose logistical challenges.
 - Davey Smith: We will have some people who can go straight in, but some people will have to do a Phase I – this is the case even for Phase II. It would require the FDA to give us some guidance.
 - Sarah Read: Also, from a network perspective, what would be the easiest to implement? Is it less efficient to have two protocols or more efficient? Maybe it's the network's decision on which is the way to go.
 - Davey Smith: Yeah that's true.
- Joe Eron: What advice is the FDA going to give? What do you hope they will tell you?
 - Judy Carrier: They might say that in humans you can do that with people who are sick and hospitalized.
 - Joe Eron: I'd agree with that.
 - Davey Smith: What exactly safety measures do they want.
 - Judy Carrier: We are in this grey zone between FDA and companies – it will not be the same for everyone. We want to move these molecules into human as quickly as possible.
 - Joe Eron: Taking people who are hospitalized to do single dose /dose escalation with mAb would be acceptable to the FDA. The question is what is the reason for companies to go outside that model? Is it logistically more difficult?
 - Ajay Nirula: Generally, in some settings with preclinical packages that company have, it's possible for FDA to push you to the hospital setting. When companies come with a more

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robust preclinical package, it's feasible to go directly into an outpatient setting. Then it becomes a desirability issue. For the study that goes into Phase II, you do want to de-risk.

- Joe Eron: The study can be designed to pause to have PK and safety for the first 10 people – it could be a run-in with 3 doses, each with 10 people. The schedule we have set up can accommodate PK post infusion. That makes sense to me. Taking outpatients and put them in a hospital when you can get the same data from patients already in a hospital – that doesn't make sense to me.
- Davey Smith: We should push for our design, which is to offer the first ~10 people for dose-finding / safety study. If we don't see a signal then we go straight in to Phase II, then the data for first 10 subjects could be considered for Phase II study.
- Judy Currier: We need to figure out how many companies would that not be adequate. If they have to do this separately, they might just do their own study.
- Davey Smith: The issue would be for those companies who want to do dose-findings. You would allow 3 doses and the company would choose a dose to proceed to Phase II. It would be complicated if it is seamless – I think we will have to consider opting in for the study. Not sure how to incorporate Bayesian rules.
- Davey Smith: At each of our stages, it would be nice to decrease the touch to our participants. Right now, both Phase II and Phase III are pretty high touch.
 - Joe Eron: It would make sense to me if we want to accrue the study rapidly to have volunteers – to have face-to-face visits for Phase III would be a challenge, operationally for the sites and logistically for the patients. The justification is not clear to me. The safer the agent the lesser you need to see the patients. I understand the goal is to move seamlessly from Phase II to Phase III
- Judy Currier: If we are able to adapt this run-in phase, operationally, what's the best way to do this? How do we accommodate that into the protocol document?
 - Michael Hughes: The major decision is whether we can do this in a highly standardized way across agents or would it be specific for each agent. If it has to be agent-specific, the easiest way is to denote an optional Phase I and include agent-specific details in the appendix. If we can do a highly standardized study – not sure how to accommodate dose-finding for each agent – then we can potentially incorporate it in the main section.
 - Joe Eron: The way it is currently designed wouldn't accommodate a Phase I for an agent that requires daily dosing (i.e., PK over 24-hour period). It would only accommodate mAb with long half-life. What Michael said makes sense.
- Judy Currier: Regarding Sandeep's comment in the chatbox ("Phase 1b dose escalation run-in is only for safety and PK and not sure we can select an efficacious dose - unless we have a PD biomarker- into the Phase 2 part. We may still send up with multiple doses in Phase 2 part") - We keep coming back to this issue of whether to have PD or biomarkers to select the dose. I think we are allowing that possibility. Interestingly one company said they would enter with only one dose.
 - Ajay Nirula: I think the small handful of patients for safety run-in. It wouldn't be particularly helpful with one dose. You would need to do dose-finding with a larger cohort.

ACTIV, Therapeutics-Clinical, ACTIV-2 Writing Team Meeting Meeting Minutes

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- Joe Eron: For the company with one dose, I presume they have enough in vitro or animal data to know multiple times above IC50 or IC90, only need PK data to confirm in humans. They have a potent enough antibody to do something like that.
- Ajay Nirula: How we are thinking about lower doses to get to more patients down the line. Regarding the question on whether it is ethical to do Phase 1b dose escalation in patients with sub-therapeutic doses, at Lilly we made the decision to be in the therapeutic range with multiple doses.
- Joe Eron: Should we incorporate language in the protocol stating that there's potential for Phase I, multiple dose, limited subset?
 - Judy Carrier: Need to get feedback from FDA on what would be the acceptable safety and dosing data for the symptomatic outpatient population.
- Karen Price: Stat team got together over the weekend to look at initial rounds of simulation. Team will reconvene tomorrow or later this week to continue the discussion. We can agree on a framework that can be embedded into the protocol, but critical successful factors would need to be defined for each asset. The intent of the framework is to allow learning. With additional data, the model would need to be updated – a master protocol like this can accommodate that.
 - Davey Smith: Thinking about graduation / termination rules for each of these components would help.
 - Michael Hughes: We know very little at the moment about the virology, the symptoms, and inter-relationships, and learning is important. We should push forward recognizing that. Once we accumulate data from the first 3-4 agents in Phase II, the learning will start to kick in. It will take some time to use virology and symptoms to make good judgement on what drugs would work in Phase III.
 - Judy Carrier: When will we know what agents will be available and when? What Michael said is an argument for putting virology in Phase III of the study to learn more.
 - Michael Hughes: That's the conversation we had over weekend. I realized that this is not a low-touch Phase III. Should we get 1-2 NP swabs to increase that information?
 - Joe Eron: I think it should be less touch than it currently is, but I can imagine a Day 7 NP swab could be very informative. I don't think you would need all the days - probably Day 1 and 7 would be enough, given the number of individuals, to make that inference.
 - Michael Hughes: How much touch do we need in Phase III? Do we need all 6 blood draws?
 - Joe Eron: I definitely don't think so.
 - Davey Smith: Each agent is going to require some safety stops. It's always been that it is supposed to be flexible to drop some of them depending on the investigative agent. If we can get the virology. You can do a baseline and depending what we see in the first 110 people, we can decide when the next NP swab would be.
 - Joe Eron: Or you could do something crazy, do some people Day 3, some Day 7, etc. and do a population PK. It would depend on the pace of enrollment. If it is quick, we will have more than 110 in Phase II.

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- Michael Hughes: You can imagine a design where you randomize the participants to come in at different days for blood draws and / or swabs so the impact on individual participant would be low. And you can do PD and PK modeling to look at the virology.
- Joe Eron: I'm all for that. It doesn't change the study design – we just need to incorporate the language in the appendix to change how frequently and how many people to come in for each specific agent. Essentially you would have a valve to adjust for Phase III. All would be included in the appendix. That makes a lot of sense and it becomes very adaptive for the agent.
- Judy Currier: It's super adaptive.
- Davey Smith: It becomes a heavy lift for the data and analysis team. I want to make sure we can come up with something that is feasible for them.
- Michael Hughes: It does make the analysis a bit harder, but the value is worth it
- Paul Klekotka: Another suggestion is to have a standard template for visits, and adjust based on agents, e.g., for this mAb maybe you can skip D3 visit.

Next Steps

- Davey Smith: We have our next CSRC call on Thursday. It would be valuable for us to get feedback on what we put in. We should get their feedback
 - Judy Currier: It would be good to hear from Sarah, Eric, and Stacey on how we continue to get feedback on the protocol and how do we accommodate different needs for different companies.
 - Sarah Read: Key is for different companies – which ones are ready to go and what are their needs. I thought Janet Woodcock is helping us to get that information. We have a meeting with her tomorrow to discuss.
 - Eric Hughes: Getting a handle on the compounds we are considering will drive a lot of our discussions.
 - Sarah Read: We can come up with specific questions for Janet to bring to the companies – not sure if she knows which companies as of now. I thought she was going to have another summit with CEO this week.
 - Stacey Adam: Summit is hopefully beyond CEO, also involve heads of R&D – they are pushing for end of week. It would be good to go into the meeting tomorrow with specific questions for Peter Stein, John Farley (representing FDA), and Janet Woodcock (representing OWS). I will also type up an email to see if we can get feedback today before the meeting.
- Judy Currier: Proceeding with the CSRC review to get NIAID input would help us get over another hurdle.
 - Sarah Read: It would be valuable to get that going.
 - Peter Kim: We don't want CSRC to represent any kind of impediment. Idea is to do CSRC sooner than later, with the understanding that there will be changes after the review.

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- Unless there are substantial changes, the team can move forward. We are asking Cyrus, as the Medical Officer, to inform the CSRC of the changes.
- Judy Currier: The big change for today is to retain the ability for specific agents to add more dose finding (i.e., Phase I run-in phase). Our preference is to do this in the same patient population for the study is conducted in.
- Davey Smith: Would also need to come up with graduation rules. It might just be the same we have for Phase II.
- Peter Kim: For Stacey and Cyrus, it would be better if we have a single channel of communication with the FDA, so they are clear that we are discussing the same study.
 - Sarah Read: ACTIV would be a faster route of communication with the FDA. We have FDA members in our working group so we should take advantage of that and ask the questions.
 - Peter Kim: I would agree with that.
 - Judy Currier: Wouldn't FDA's opinion also depend on the investigative asset? It would be hard to get generic responses. How do we move forward and propose specific agents in the discussion?
 - Stacey Adam: That would come down to the OWS team and Janet Woodcock. Tomorrow's call could be helpful in this regard.
 - Lisa LaVange: In general, for master protocols, you go back to the FDA with additional information with each additional drug. The FDA is used to operating that way. It depends on how many we start with. Think about the 9 we start with so we can get the common denominator for the first round.
 - Peter Kim: When you communicate with FDA, please keep Cyrus and MaryAnne informed.
- Judy Currier: We might need to clarify who's on the Steering Committee - who are the deciders and who are the all the stakeholders we need to get feedback on, how operationally this is going to work.
 - Lisa LaVange: One suggestion I have: If you have algorithm, use algorithm as much as you can. Take the human being out of it - of course that wouldn't apply for safety.
 - Stacey Adam: Part of the purpose of having our previous meeting with mAb experts is to decide on the minimum entry criteria. If the drug checks the box, we are not going to be very stringent. It would be a box-checking at that point
- Peter Kim: It seems like the way the study is designed to accommodate a single mAb. Has the mechanism been built in to consider multiple / combination of antibodies, at least at the Phase III level?
 - Lisa LaVange: You have the infrastructure to do it. You just need to add in the appendix for A+B vs. placebo instead A. But that would have safety issues. If a drug looks good, what does it take for it to become standard of care. Maybe in this case, adding antibodies would make sense.
 - Judy Currier: I envision some companies would come to us to study multiple antibodies.

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- Joe Eron: There might be safety issues. Operationally it would fit right into this.

Chatbox

From Sandeep Menon to Everyone: 02:31 PM

Phase 1b dose escalation run-in is only for safety and PK and not sure we can select an efficacious dose (unless we have a PD biomarker) into the Phase 2 part. We may still send up with multiple doses in Phase 2 part.

We may still need multiple doses in phase 2 part...

Is it also ethical to do phase 1b dose escalation in patients with sub-therapeutic doses?

Thanks Ajay

From Davey to Everyone: 02:45 PM

I don't think we would accept sub-therapeutic dose

ACTIV, Therapeutics-Clinical mAb Steering Committee, Meeting Minutes

Friday, May 22nd, 2020

Action Items

Action Items		
	Information	POC
1	Follow up with INSIGHT on the decision of having them as the lead network for ACTIV-3	Stacey Adam
2	Follow up with NHLBI network to discuss the possibility and next steps to partner in ACTIV-3	Stacey Adam
3	Share the draft ACTIV-2 master protocol with mAb expert group for comments	Stacey Adam
4	Share with the group data on viral data conducted at (b) (4)	Carl Garner
5	Share with the group virologic testing data on the hydroxychloroquine trial	ACTG Team

Key Takeaways

- Team has decided on INSIGHT as the leading network for ACTIV-3.
- The team will ask NHLBI to partner with INSIGHT and include them in the protocol writing and the operations planning if they accept to partner.
- One of the final pieces needed for the protocol is to figure out what kind of data the companies will be generating prior to joining the trial. This information will help our group set the baseline for the trial entry. The group decided to send the protocol to the group that will be designing the minimum entry criteria to get feedback on what they thought since the represent companies with mAbs that would likely be ready this year.
- For both mAbs master protocols (outpatient and inpatient), team has decided to have a single DSMB controlled by NIAID.

Notes

Lead Network for ACTIV-3

- Sarah Read: I am more familiar with INSIGHT. I'm confident that they can do this and will make this a top priority. There are also advantages of being able to (b) (5) both the outpatient and the inpatient at NIAID. Although I have heard from (b) (6) who said they will also make this as high priority and have the flexibility (b) (5)
- Sam Bozzette: What's the openness for them to be partners and not the lead?
 - Sam Bozzette: He felt that INSIGHT would only participate if they could lead and wondered if they would actually partner.
 - Sarah Read: They would participate regardless and provide intellectual input.
 - Joan Butters: She felt that NHLBI would only participate if they could lead. Though she acknowledges that they have also articulated a willingness to partner.

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- Judith Currier: Given how fast things move, who are the investigators from NHLBI leading the studies. We have a better understanding from INSIGHT.
- Carl Garner: Both seem willing to take the lead. I've been impressed with how they work through issues and implement. My vote would be to have INSIGHT as the lead and try to have PETAL to partner with them.
 - Janet Woodcock, Sam Bozzette, and Libby Higgs support that approach.
 - Joan Butterton: From all the emails exchanges it seems like we are leaning in the direction of having INSIGHT as the lead network.
- *Judith Currier: Alignment between inpatient and outpatient – would it make sense to have some representative from the outpatient be part of the team?*
 - Libby Higgs: It would make good sense to have inpatient on the outpatient team and vice versa to help with alignment and share lessons. Outpatient is a little ahead in terms of product which would be for the inpatient team. Another thing we discussed is setting up a CAB and a DSMB for these trials, assume we can share one across both.
 - *Stacey Adam: Question for Judith – Is the plan to have the outpatient master protocol going to ACTG usual DSMB or are you amenable with having a joint DSMB for both of these trials?*
 - Judith Currier: Peter is envisioning it going to a NIAID DSMB that has been convened which has been used for other COVID trials, but open to alternative solutions.
 - Libby Higgs: It would be preferred to a single one.
 - Sarah Read: NIAID convened a DSMB. A number of them with a number of expertise. We can build off an existing one and add an expertise for COVID or build a new one. But it would make sense to have a single DSMB for both trials.

Remaining questions for ACTIV-2

- Lisa LaVange: With the networks, we want to emphasize with them about conducting master protocol trials that we don't want to start a protocol every time a drug comes in.
 - Stacey Adam: There may be some oversight committee that we are assisting with in the long run to help.
 - Janet Woodcock: Agree with what Lisa said. We would still need to work through some major design issues. We are consulting with firms and see what development programs they plan to do. One issue is dose-finding, the regulators have a strong preference for a more robust dose-finding study (e.g., 50 patients per arm, four different doses, etc.). Either companies run that and we run the Phase III, or we organize some study to graduate candidates into Phase III. Input from the company would be helpful in deciding the path forward. Another is the statistics - we need to decide whether have a common control group, etc. These issues need to be resolved before talking about an oversight structure.
- Carl Garner: We need to maintain some group discipline. We wrote a letter to executive committee to ask them to get all the sponsors together to establish a master protocol to have common

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inclusion, endpoints, number of control arms, etc. We should not waiver on whether this is a master protocol otherwise we wasted time.

- Judith Currier: We have landed this morning that this is a master protocol Phase II/III. Drugs would have to have some previous experience to get in. They will be evaluated in Phase II before moving into Phase III. We can share what we have with the company and get their opinions instead of asking them what they want to do.
- Janet Woodcock: That's fine and we should ask FDA too. If they are going to do a robust dose-finding study, and if we are going to do another bar for efficacy into Phase III, it may introduce a second step. I can't see them do a virologics with four-arms and we repeat it with two arms.
- John Farley: Agree with Janet. It feels like we are adding another step, but if the four-arm studies are not uniform, then we don't have a way to decide who gets to be included in Phase III. The most important stakeholder would be the companies as they are the customers of the protocols.
- Sam Bozzette: *Can we tell them what we need?* If we go with the route of having a prior dose-finding study, then we will need to introduce some guidelines. But different companies have different levels of resources and it would be more economical and efficient for us to have a dose-finding platform.
- Janet Woodcock: It would be possible for us to offer the dose-finding study as the initial stage of ACTIV-2. At some point, once we have enough candidates for Phase III, we can stop that and have them go to BARDA, for example. The goal is to move things as quickly as possible.
- Lynn Marks: Shame would be to lose subjects in Phase II as part of Phase III for speed. Need to make sure they are harmonized.
- Lisa LaVange: Our remit was to design a seamless Phase II/III trial and had nothing to do with a rigorous dose-finding. Starting with Phase III would lose things.
- Judith Currier: Some of the companies are doing Phase I are doing so in hospitalized patients so they can join this trial. We need to check with the company to see how they want to do it.
 - Janet Woodcock: I think they are doing Phase I safety in hospitalized patients and are planning to do a robust dose study after.
 - Lisa LaVange: If you offer this to the company and they would drop their Phase II plan and have us do it.
- Janet Woodcock: What is the minimum FDA would accept (i.e., safety, does) would FDA accept to go into a Phase III?
 - John Farley: FDA intends to be more flexible in ill patients.
 - Janet Woodcock: Say they have done an extended Phase I with multiple doses, some virologic data, pK, none was definitive. And they want to pick two doses for master protocol.

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- John Farley: With the vision it would be ok. Initial study would be hospital setting. Would be a good question for the company.
- Sam Bozzette: Clinical situation is so much different. I have no confidence with the virology. I would accept suppression or clinical resolution – suppression alone in a hospital setting would not qualify for the study.
- Libby Higgs: Might be too early to disregard viral load as an early surrogate?
- Joan Butterson: I agree that it would be appropriate to engage with the industry at large as they are all having the same conversation.
 - Janet Woodcock: The idea is for them to do an extended Phase I or some sort to have some dose tolerance; People would be comfortable with us studying two doses and have an 'or' - the only way to have better understanding is doing a larger efficacy study.
- Stacey Adam: We have assembled experts on mAb (from companies, NIAID, and academics) – is that the right group to review and comment on the master protocol as is? We have our first meeting on Tuesday.
 - Carl Garner: These would be the right companies. We need to go in with this is what we are trying to do, this is our purpose of the trial, this is how we plan to get there. We don't want them to go off and do trials on their own because it creates competition. Companies will be flexible as this group has the reach and capabilities.
 - Joan Butterson: I'm concerned about losing momentum. We have a reasonable design to go through this approach.
 - Libby Higgs: *Can we convene with the group sooner over this weekend?* The experts aren't willing to meet over the weekend.
 - Judith Currier: It would be ok to share the current protocol for their input.
 - Janet Woodcock: It would also be important to have FDA on the call with the companies to clarify what's accepted from the regulatory perspective.
- Lynn Marks: From the companies' perspective, why would they want to join this network? "The government would slow me down. There's no guarantee to become the first in line with a positive for standard of care then I'm stuck in the limbo of master protocol". How do we address that? We would need to work on the messaging in advance.
 - Janet Woodcock: We need to advance and test as many as possible. With a master protocol, we can move a lot of them and evaluate them all at once. Maybe in the future may need to run a non-inferiority study.
 - Libby Higgs: Master Protocol accommodates lack of supply in your control arm.
- Janet Woodcock: *Do we know where the funding for ACTIV-1 is coming from?*
 - Stacey Adam: We don't know yet.
- Libby Higgs: *Are we still considering NHLBI?* Yes. However, we can get the agents into network of large quantity of patient populations we have planned.

**ACTIV, Therapeutics-Clinical mAb Steering Committee,
Meeting Minutes**

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Chatbox

From Sarah Read to Everyone: 02:37 PM

Sorry I'm having issues with audio (not hearing people). I'm going to dial in by phone.

From (b) (6) to Everyone: 02:52 PM

agree

how sure are we that viral suppression is a good marker?

From Lisa LaVange to Everyone: 03:08 PM

I am late for my next meeting — sorry to leave this good discussion.

ACTIV, Therapeutics-Clinical Master Protocol Subgroup, Meeting Minutes

Friday, May 22nd, 2020

Action Items

Action Items		
	Information	POC
1	Incorporate drug-specific information submitted from (b) (4) and (b) (4) into ACTIV-1; share updated draft of ACTIV-1 with the writing team to review	Stacey Adam
2	Schedule ACTIV-1 review meetings with the writing team on Tuesday and Thursday next week	Stacey Adam
3	Share drug-specific information or (b) (4) with Stacey to be incorporated into ACTIV-1	David Bharucha
4	Update the company partners with decisions on network selection, countries for studies, etc. as they are made	Stacey Adam

Notes

Opening

- Today's meeting is shortened from 1hr to 30 minutes.
- For ACTIV-1, wanted the team to meet the company representatives to develop a strategy to finalize ACTIV-1
- For ACTIV-2, we have split that to a separate group for a more tactical discussion

ACTIV-1: Discussion with Companies

- Sarah Read and Eric Hughes: Welcome all company representatives to the call. Looking forward to working closely.
- Introduction to the Teams
 - (b) (4), (b) (6) : VP of Clinical Development of (b) (4)
 - (b) (4), (b) (6) : Head of Immunology (b) (4)
 - (b) (4), (b) (6) : Development Lead for (b) (4)
 - (b) (4), (b) (6) : Medical Lead for (b) (4) n
 - (b) (4), (b) (6) : Compound Development Team Lead for (b) (4)
- Update of where we stand with the protocol
 - Have received updates from (b) (4) team for drug specific information for the protocol. (b) (4), (b) (6) confirmed that drug-specific information from (b) (4) will be submitted by early next week.
 - Stacey will work over the weekend and early next week to compile drug specific information from the companies. Can have a rough working protocol for everyone to review by Tuesday, especially if (b) (4) has their info in by Monday
 - We are interviewing and engaging with networks – meeting today with the NCATS TIN (60 sites within US and can be up and running quickly). We had a few discussions with NHLBI; should have the network pinned down by end of next week

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- (b) (4), (b) (6) : *Would one of the selection criteria for the network be the time it takes for them to get up and running? We are considering networks who can 25-50% site up and running within a few weeks.*
- (b) (4), (b) (6) : *Studies in US only or global? Hope is to conduct trials globally as the virus is migrating. Would go through the route to get your trials done the most efficiently*
- Next steps:
 - Stacey will schedule a few meetings next week – on Tuesday and on Thursday to review and discuss with the goal to finalize the protocol.
 - (b) (4), (b) (6) and (b) (4), (b) (6) : *Twice a week cadence and 36 hours in between is reasonable*
 - Stacey Adam: In terms of participation in these review meetings - don't expect participation from the full group but welcome anyone who is interested to continue being involved in the review and refinement of the protocol
 - (b) (4), (b) (6) : *Who would be on the oversight committee? At least 1 statistician for continuity, 2-4 members from this committee who have been involved in drafting, representatives from the participating companies, 2-3 members from the network representatives*
 - Pamela Tenaerts: *Have we incorporated any quality by design principles into designing the protocols (e.g., streamlining the protocol and focusing on what matters)?*
 - (b) (4), (b) (6) : *My understanding is that most of the protocol has already decided, and we are not changing the spirit of the protocol at this point?*
 - Stacey: Protocol is 80% written; won't change too much; can consider specific tweaks and small refinements to streamline the protocol
 - Sam Bozzette: CTTI has a nice document summary that we can click through and check.
 - Joan Butters: Have followed the guidelines for ACTT-1 and 2
 - Stacey Adam: The aim to activate ACTIV-1 by early to mid-June. Limiting factor would be locking down the network
 - (b) (4), (b) (6) : *What does activate mean? FDA approved, network approved, sites able to enroll. We've heard that 48 hours post activation patients can be enrolled.*
 - (b) (4), (b) (6) : *If we are going to move that fast, I will need specific information for what you need from drug perspective what you need from drug (e.g., certificate of quality, how much drug is needed, where the drug will be shipped). The sooner the better.*
 - (b) (4), (b) (6) : *The sooner we have a decision around what country we might be going into, it would help with instructions such as drug labeling.*
 - (b) (4), (b) (6) : *The network can possibly do the labeling instead of the company? That would depend on the network. Many NIH networks have drug distribution centers. If that's the case, central pharmacies would do the labeling.*
 - (b) (4), (b) (6) : *For (b) (4), having the network do the labeling would be preferable.*